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ACTH OR ADRENOCORTICAL STEROID THERAPY OF PROTEINURIA IN ADOLESCENTS AND IN ADULTS*

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The high percentage of remissions in the childhood form of the nephrotic syndrome treated with massive pharmacologic dosages of ACTH or adrenocortical steroids obtained in our clinic and elsewhere (Burke[1], Danowski *et al.*[3], Galán and Maso[4], Greenman and Danowski[5,6], Greenman, Weigand and Danowski[7], Lange *et al.*[8], Mateer *et al.*[9,10], Parrish, Watt and Howe[11], Riley *et al.*[12], Roscoe[13]) has raised the hope that the proteinuria of some forms of renal disease in older children and in adults might also be beneficially influenced. Complete and, to date, persistent disappearance of proteinuria with entirely normal urinary findings has been noted during such therapy in about 15% of the older children and adults in an unselected population of proteinurics under our care.

Materials and Methods. Fifty-four patients, 36 males and 18 females, ranging in age from 11 to 69 years received ACTH† or adrenocortical steroids for one to 30 months or longer in pharmacologic dosages as indicated in Tables 1, 2 and 3.

In 30 of these the probable nature of the renal lesion was established by a percutaneous needle biopsy of the kidney. In 4 others the diagnosis was based on necropsy findings. This group of 34 patients consisted of 11 patients with membranous glomerulonephritis, 5 with subacute glomerulonephritis, 9 with

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†All of the ACTH employed in the clinic patients in this study was generously supplied by the National Drug Company through Drs. Gustav Martin and William Swain.

TABLE 1.—TREATMENT AND LABORATORY FINDINGS IN NINE PATIENTS IN WHOM A COMPLETE REMISSION OCCURRED WHICH HAS PERSISTED TO DATE

Pt. Age/sex	*Duration*	*Diagnosis*	*Therapy*	*Time*	*B.P.*	*Edema*	*Urine prot.*	*NPN mg./100ml.*	*Serum alb. gm. %*	*Serum glob. gm. %*	*Serum chol. gm. %*	*CNNE clear.*
E.McG. 25 F	3 y ?	L.E.D.*	200u§ 28d 200u MTW 13m	ā ℞ p̄ ℞‡ 3 y	118/74 110/60 104/70	3+ 3+ 0	4+ 3+ 0	28 53 27	0.73 1.19 3.79	3.10 1.19 2.81	990 253 263	135
V.G. 32 F	1 y	Membr. G.N.*	200u 28d 0	ā ℞ p̄ ℞ 3 m	140/100 130/90 125/70	2+ 2+ 0	4+ 0 0	27 28 Ne	1.29 1.72 3.40	2.72 1.81 1.90	709 442 230	
A.B. 25 F	6 w	Neph. syn.	200u 28d 50–400C MTW 16m	ā ℞ p̄ ℞ 2.75 y	120/80 139/90 104/66	4+ 0 0	4+ 0 0	35 26 31	0.43 3.20 4.04	2.92 2.33 3.68	673 472 215	
C.A. 25 M	3.25 y	Pyeloneph.*	200u 24d 0	ā ℞ p̄ ℞ 1 m	140/100 160/98	4+ 0 0	4+ 0 0	34 29 36	0.27 2.24 3.63	3.31 2.69 3.49	461 220 258	185
J.K. 28 M	7 m	Sarcoid*	200u 28d 100–300C MTW 11m	ā ℞ p̄ ℞ 4 y	120/88 130/78 124/80	1+ 0 0	3+ 4+ 0	33 23 36	1.64 1.76 4.14	2.63 2.78 3.57	384 378 290	287
C.R. 17 M	10 w	Neph. syn.	200u 28d 100u MTW 12m 12T q.d. 3m	ā ℞ p̄ ℞ 1.6 m	160/80 160/100 130/80	2+ 0 0	4+ 1+ 0	85 48 40	1.08 4.07	1.77 3.34	402 252	101
J.H. 38 M	10 m	Neph. syn.	200u 28d 0	ā ℞ p̄ ℞ 4.7 y	160/110 140/90 130/80	3+ 0 0	4+ 0 0	41 37 40	2.13 2.21 4.07	1.97 2.46 3.34	252	
C.Z.† 13 F	1 y	Neph. syn.	200u 28d 100u MTW 5m 200u MTWThF 19m	ā ℞ p̄ ℞ 2.6 y	112/72 112/70 100/70	1+ 0 0	4+ 0 0	49 43 30	0.29 TP 6.0 3.91	2.41 1.96	824 250 235	95
J.Hy. 32 M	5 m	Membr. G.N.*	200u 27d 200u MTW 2m	ā ℞ p̄ ℞ 3 m	160/110 150/90 190/100	2+ 0 0	3+ 0 0	35 35	2.34 3.66	3.04	218 178	

* Diagnosis from kidney biopsy
‡ Refers to end of initial course of therapy
† Still under treatment
§ u—Units ACTH; C—mg. cortisone; T—mg. Triamcinolone; P—mg. Prednisone; Duration: d—day; m—month; y—year

chronic glomerulonephritis, 3 with pyelonephritis, 2 with intercapillary glomerulosclerosis, and one each with lobular nephritis, arteriolar nephrosclerosis, sarcoidosis, and possible disseminated lupus erythematosus (Table 4).

In the remaining 20, only clinical impressions are available (Tables 1, 2 and 3). Thus, a clinical diagnosis of nephrotic syndrome without hypertension was made in A.B. and C.Z. who had normal blood pressure, edema, heavy proteinuria, hypoalbuminemia and hypercholesterolemia. The nephrotic stage of glomerulonephritis was presumed to be present in C.R., J.H., R.S., A.W., J.W., and J.K. who had hypertension, microscopic hematuria and azotemia in various combinations in addition to the above findings. Acute glomerulonephritis was believed to be the diagnosis in J.Ha. whose illness was characterized by hypertension, mild azotemia, proteinuria, cylindruria, and hematuria of 2 weeks' duration. Chronic glomerulonephritis was inferred to be present from the usual criteria of hypertension, impaired renal function, proteinuria, microscopic hematuria and presence of granular casts in the remaining 11 patients: E.Y., H.L., B.M., D.B., W.T., D.H., P.S., M.M., R.S., S.S., and F.B. These and the preceding groups of patients are listed in Tables 1, 2 and 3 together with pre- and post-therapy and follow-up findings in urine, blood and serum.

Initial therapy usually consisted of 200 units of depot ACTH, though amounts ranged from 50 to 500 units, given daily in divided dosage for 28 days or longer while on a diet rigidly restricted in sodium but providing 150 to 200 mEq. (Greenman and Danowski[5], Mateer *et al.*[9]). Patients F.C. and P.T. were treated with triamcinolone only.

As indicated in the Tables, in many of the patients subsequent treatment with ACTH, cortisone, hydrocortisone, prednisone or triamcinolone on an intermittent or a continuous basis was undertaken in the hope of inducing a remission in those who had not responded or of preventing a recurrence in the others. The dosage of ACTH employed for these purposes was usually 200 units of depot material daily for 3 successive days of each week. In the case of cortisone, 200 to 400 mg. were usually given daily on a 3 days on and 4 days off schedule, though in some patients continuous therapy was employed. The same scheme was followed with prednisone and triamcinolone, though the dosages were less. During such intermittent therapy restriction of sodium intake was advised only when edema appeared. This was less often necessary with prednisone and triamcinolone than with ACTH, cortisone, and hydrocortisone. Antibiotics were given only as infections occurred. Anticholinergic drugs or antacids were not routinely administered.

Prior to, during or at intervals after therapy, venous blood was analyzed for sugar and nonprotein nitrogen levels and venous serum for CO_2 content and the concentrations of chloride, sodium, potassium, calcium, phosphorus, and cholesterol by methods in regular use in this laboratory (Danowski *et al.*[2]). Routine urinalyses were obtained. Proteinuria was quantitated by the heat-acetic acid method by one of us and less often by macro Kjeldahl determinations with correction for the nonprotein nitrogen. The clearance of endogenous creatinine was also measured at intervals. Because of the sheer bulk of these data, only selected portions germane to the aspects discussed in this paper will be presented.

Patients receiving maintenance steroid or ACTH were examined for tuberculosis by roentgenograms of the chest and by serial patch tests; morning body weights and temperatures at 4 p.m. were obtained daily and a postprandial urine was examined each day with TesTape for glucose; these findings together with any symptoms, signs, alterations in body hair, menses, and the like were recorded by the patient and reviewed by the physician at each 2- or 4-week visit.

Results. A. CLINICAL OUTCOME. The 54 patients in this series can be divided into three groups on the basis of changes in the proteinuria: 1) 9 patients in whom the proteinuria and all abnormal clinical and laboratory manifestations disappeared completely (Table 1); 2) 21 patients in whom the heavy pre-treatment proteinuria decreased at the end of the initial course to 1+ or trace but did not disappear (Table 2); and 3) 24 patients in whom the proteinuria was only slightly affected, if at all (Table 3).

Remission in the first group occurred either after the initial 28-day course of therapy (A.B., C.A., C.R., V.G., J.H., C.Z., and J.Hy. in Table 1) or after an initial course and intermittent ACTH for a prolonged period (E.McG. and J.K. in Table 1). Of the 9 patients

† Still under treatment
§ u—Units ACTH; C—mg. cortisone; T—mg. Triamcinolone; P—mg. Prednisone; Duration—day; m—months;

TABLE 2.—TREATMENT AND LABORATORY FINDINGS IN 21 PATIENTS IN WHOM PROTEINURIA DECREASED TO 1+ OR LESS AT END OF INITIAL COURSE OF THERAPY

Pt. Age/sex	Duration	Diagnosis	Therapy	Time	B.P.	Edema	Urine prot.	NPN mg./100 ml.	Serum alb. gm. %	Serum glob. gm. %	Serum chol. gm. %	CNNE clear. ml./min.
B.S. 19 F	10 m	Membr. G.N.*	200u 28d 200u MTW 3w 100u MTW 3m 36T MTW 1.25m	ā R p̄ R 1.25m	130/80 134/80 132/81	1+ 0 0	2+ Tr Tr	 28 37	3.2 4.18 3.57	2.4 5.37 3.51	288 209 238	 45
R.S. 27 M	7 y	Neph. syn.	200u 28d 160u MTW 1.3y	p̄ R p̄ R 1.3 y	142/84 130/98 128/78	4+ 0 0	4+ 1+ Tr	64 81 39	1.1 1.1 3.07	3.0 3.0 2.99	755 755 308	
A.W. 45 M	5 m	Neph. syn.	200u 28d 0	ā R p̄ R 3.17y	145/85 122/84	4+ 0 0	4+ 0 Tr	45 30 35	1.22 3.04 4.64	3.21 2.39 2.32	667 350 283	
J.Ha. 34 F	2 w	Ac. G.N.	200u 28d 0	ā R p̄ R 10 m	140/106 104/80 120/70	2+ 0 0	4+ 0 Tr	45 45 34	3.03 3.22 3.92	4.32 2.71 3.33	249 141 201	 114
E.Y. 26 F	1 y	Chr. G.N. Rh. Arth.	200u 28d 85.5C 6m	ā R p̄ R 3.5y	138/92 120/90 130/80	2+ 0 ±	3+ Tr Tr	32 28 31	4.10 3.24 3.04	3.08 3.16 3.48	210 208 239	 48
M.McC. 17 M	10 m	Membr. G.N.*	200u 28d 200u MTW 1m 200u MTWThF 4m 100u MTW 1y 3w	ā R p̄ R 1.17y	132/80 146/80 122/80	2+ 0 0	4+ Tr 1+	31 34 39	0.73 2.70 4.00	3.10 2.09 2.06	990 235 345	 133
H.L. 24 M	5 y	Chr. G.N.	200u 25d	ā R p̄ R 6 m	150/90 130/90 132/80	0 0 3+	2+ 1+ 3+	36 34 45	3.52 3.72 3.79	2.85 2.71 2.40	134 291 235	 110
B.M. 58 F	5 y	Chr. G.N.	200u 6d T48 3d T60 18d	ā R p̄ R 3 m	220/95 164/84 168/76	4+ 3+ 3+	4+ 1+ 3+	38 36 46	2.34 1.86 2.61	2.32 2.42 2.27	305 315 292	 21
F.C. 19 F	6 y	Membr. G.N.*	T60 24d T32 2d T24 21d	ā R p̄ R	180/110 126/82	4+ 3+	4+ 1+	50 80	2.73 1.18	2.92 4.02	407 250	 59
H.H. 15 F	2 y	Chr.G.N.*	200u 28d 200u MTW 100u MTW 100u MT	ā R p̄ R 13m	150/100 120/90 140/90	0 0 0	4+ 1+ 3+	34 38 31	1.3 2.2 2.74	1.7 1.7 2.83	428 214 304	
A.B. 40 F	2 m	Chr. G.N.*	200u 36d	ā R p̄ R 1.25y	250/110 190/100 190/110	4+ 1+ 0	4+ 1+ 1+	 45 39	0.95 1.46 3.24	3.24 2.67 3.24	558 415 [illegible]	
C.S.	11 y	Chr. G.N.*	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]

A.B. 40 F	2 m	Chr. G.N.*	200u	36d	♂ R ♀ R 1.25y	250/110 190/100 190/110	4+ 1+ 0	4+ 1+ 1+	 45 39	0.95 1.46 3.34	3.24 2.67 3.88	558 415 428	
C.S. 32 M	11 y	Chr. G.N.*	200u	28d	♂ R ♀ R 3 y	140/104 134/92 160/80	2+ 0 ±	 Tr 2+	41 46 27	3.76 2.64 3.69	3.08 2.77 3.73	275 243 342	60
H.R. 20 M	2 y	Subac. G.N.*	200u	28d	♂ R ♀ R 6m	120/70 130/80 134/70	0 0 0	1+ Tr 1+	40 45 38	3.65 2.60 3.18	3.65 3.77 3.46	238 198	87
D.B. 32 M	2 y	Chr. G.N.*	200u	23d	♂ R ♀ R 1.25y	150/110 108/80 142/100	0 0 0	3+ Tr 1+	 47	3.8 3.95	2.5 2.80	238 300	
I.H. 36 F	19 y	Chr. pyel.* neph.	30P MTW 2m 30P Daily 1m 200u 22d T16 1m		♂ R ♀ R 1.6y	135/85 140/80 118/64	4+ 4+ 2+	4+ 1+ 1	32 39	1.4 1.90 2.45	1.9 1.40 2.81	444 259 398	108
D.B. 29 F	3 y	Chr. G.N.	200u	28d	♂ R ♀ R 4y	150/100 134/84	0 0 0	2+ 1+ 2+	32 38 36	3.82 3.94 3.76	3.40 3.15 2.39	267 449 475	83
G.P. 38 M	6 w	Subac. G.N.*	100u 200u 200u 200u MTW 6m	28d 28d 28d	♂ R ♀ R 3.25y	170/104 140/90 185/92	4+ 0 3+	4+ Tr 4+	33 45 224	0.9 1.57 1.60	1.9 2.25 1.70	554 455 191	56
J.W. 56 M	7 m	Neph. syn.	200u 40P 9m	27d	♂ R ♀ R 4.8 y	140/84 110/80 152/80	4+ ± 0	4+ 1+ 4+	41 31 52	1.70 1.38	3.02 3.40	571 296	
W.T. 29 M	5 y	Chr. G.N.	200–250u	25d	♂ R ♀ R 8 m	120/70 138/88 148/110	1+ 0 0	4+ Tr 4+	49 78 45	3.06 3.31 4.1	3.70 1.70 0.09	348 227	
S.M. 26 F	8 y	Membr. G.N.*	200u 30P MTW 2m 30P MTW 1y	34d	♂ R ♀ R 1.25y	140/90 150/100 100/52	4+ 2+ 0	4+ Tr 3+	 54 32	2.0 3.4 3.63	1.3 2.89	314 267 248	158
R.S. 22 M	4 y	Chr. G.N.*	200u 200u MTW 7w 160F MTW 11m 160F MTW 5m	26d	♂ R ♀ R 2.5y	170/118 146/80 156/90	0 0 0	4+ 1+ 4+	35 41 39	2.71 2.89 3.60	2.01 2.52 2.61	449 358 532	14

*Diagnosis from kidney biopsy
Shaded cases have since died (see Table 7)

TABLE 3.—TREATMENT AND LABORATORY FINDINGS IN 24 PATIENTS IN WHOM PROTEINURIA DID NOT DECREASE TO 1+ OR LESS AT END OF INITIAL COURSE

Pt. Age/sex	*Duration*	*Diagnosis*	*Therapy*	*Time*	*B.P.*	*Edema*	*Urine prot.*	*NPN mg./100 ml*	*Serum alb. gm. %*	*Serum glob. gm. %*	*Serum chol. gm. %*	*CNNE clear. ml./min*
H.P. 51 M	3 m	Lobular G.N.*	200u 28d	ā R p̄ R 1.25y	180/110 120/90 170/120	4+ 2+ 0	4+ 2+ 4+	 44	1.1 1.50 1.19	2.2 1.90 3.85	462 350 365	 44
G.W. 49 M	1 y	Membr. G.N.*	200u 28d 200 MTW 3m 40P q.d. 2m	ā R p̄ R 2.4y	178/88 130/80 142/90	4+ 2+ 2+	4+ 3+ 3+	33 32 51	2.18 1.93 1.31	2.83 2.24 3.33	684 375 703	 67
J.G. 32 F	7 m	Membr. G.N.*	200u 28d 200E MTW 1m 200u MTW 7m	ā R p̄ R 1.8y	126/90 158/86 136/92	4+ 1+ 3+	4+ 3+ 3+	34 35 71	1.37 1.66 3.12	3.18 2.65 1.90	673 305 402	 22
J.V. 44 M	6 m	Membr. G.N.*	200u 28d 60T 28d 200u MTW 2m 60T MTW 2m 30T MTW 2m	ā R p̄ R 1y	128/84 118/98	3+ 1+ 1+	4+ 4+ 3+	35 40	1.4 2.82	2.6 1.79	282 345	 130
E.D.'A. 19 F	19 m	Chr. G.N.*†	100u 28d	ā R p̄ R	152/118 116/76	4+ 1+	4+ 2+	37 43	1.39 1.96	2.59 2.43	657 466	 7
W.C. 31 M	11 m	Intercap.* G. Scler.	200u 20d 300–500C 35d	ā R p̄ R 1.17y	172/110 150/100 130/95	± ± 0	3+ 3+ 4+	60 83 64	2.45 2.30 1.96	3.55 3.03 2.93	306 375 361	
D.G. 39 M	2.5 y	Intercap.* G. Scler.	200u 28d	ā R p̄ R	210/112 200/110	3+ 0	4+ 2+	81 89	2.72 2.51	4.08 2.18	476 198	 14
A.D. 34 M	4 y	Arteriolar* Neph. Scler. D.M.	200u 35d	ā R p̄ R 3 m	206/130 160/88 110/60	4+ 3+ 1+	2+ 3+ 2+	79 129 85	1.41 2.14	3.28 2.62	489 123	 12
D.H. 18 F	2.5y	Chr. G.N.	200u 25d	ā R p̄ R 5 y	142/100 140/95 122/80	0 0 0	4+ 2+ 2+	64 50 40	3.54 2.73 3.28	2.43 2.18 2.62	312 294 429	 45
P.S. 31 M	5 m	Chr. G.N.	200u 28d	ā R p̄ R 7 m	140/92 120/60 106/68	0 0 ±	1+ 1+ 1+	37 44 40	3.81 2.54 3.47	2.96 2.21 2.79	171 205 240	
G.K. 34 M	22 y	Chr. G.N.*	200u 23d 200u MTW	ā R p̄ R 3 y	206/122 154/112 192/110	0 0 0	1+ 1+ 1+	116 52 BUN 230	1.77 1.88 4.10	3.76 2.52 1.30	200 270 	 26
M.M. 23 M	3 y	Chr. G.N.	200u 26d	ā R p̄ R	202/110 190/120	0 0	2+ 2+	86 172	3.81 3.10	2.75 1.70	263 195	

M.M. 23 M	3 y	Chr. G.N.	200u	26d	ā R p̄ R	202/110 190/120	0 0	2+ 2+	86 172	3.81 3.10	2.75 1.39	263 125	
G.W. 69 M	1 y	Subac. G.N.†	200u	22d	ā R p̄ R	176/110 160/98	4+ 3+	4+ 3+	62 97	1.53 0.72	3.18 1.91	525 223	
C.C. 46 M	28 y	Chr. G.N.†	200u	7d	ā R p̄ R	208/144 144/100	4+ 4+	4+ 4+	82 331	3.24 3.17	2.43 2.03	229	17
P.T. 20 M	2 y	Membr. G.N.*	T40 MTW 60d		ā R p̄ R	110/80 122/80	0 0	4+ 3+	37 36	3.71 4.63	1.94 2.42	175 270	94
E.B. 30 M	3 m	Membr. G.N.*	200u	22d	ā R p̄ R 1.5 y	140/80 130/70 130/60	4+ 0 0	4+ 3+ 2+	59 85	1.64 1.70	2.12 1.87	250 163	
J.L. 55 M	7 m	Chr. G.N.*	500u	31d	ā R p̄ R 10m	230/140 170/110 190/110	0 0 0	1+ 1+ 4+	85 91 75	3.43 2.88 3.11	2.78 2.27 2.79	223 135 255	20
R.L. 42 M	6 m	Subac. G.N.† Ac. pyelo. Neph.	50–100	49d	ā R p̄ R 1.1y	182/98 180/90	3+ 2+	4+ 4+	46 83 146	2.63 1.92 4.27	3.17 2.83 3.23	171 267	
A.Y. 34 M	8 y	Subac. G.N.*	200u 200u	21d 28d	ā R p̄ R	130/84	4+ 4+	4+ 4+	32 82	0.61 1.8	2.76 2.9	830	47
H.T. 56 M	1 y	Pyelo. Neph.	200u	28d	ā R p̄ R	130/80 100/70	4+ 4+	4+ 3+	64 29	1.6	2.5	500	
J.K. 54 M	7 m	Neph. Syn. D.M.‡	200u	10d	ā R p̄ R	168/110 140/66	4+	4+ 4+	65 119	1.71 0.82	2.50 2.75	830 353	9
R.S. 31 M	20 y	Chr. G.N.	200u	7d	ā R p̄ R	210/330 200/120	0 0	4+ 4+	156 228	4.77 4.67	2.57 2.62	182 270	
S.S.** 11 F	2 y	Chr. G.N.	200u 28d 200u MTW 4m T 24 6m		ā R p̄ R 1 y	152/102 128/96 122/82	1+ 0 0	4+ 2+ 1+	54 40 34	1.99 2.97 3.86	2.85 1.91 2.75	251 236 203	49
F.B. 14 M	4 y	Chr. G.N.	200u 27d 200u MTW 4m 100u MTW 10m		ā R p̄ R 1 y	162/104 120/80 155/110	1+ 0 0	4+ 2+ 1+	42 28 26	2.83 3.24 3.34	1.46 3.24 2.66	565 350 362	96

*Diagnosis by kidney biopsy
†Diagnosis by necropsy
‡Appeared during therapy
Shaded cases have since died

whose proteinuria cleared, 2 had a histological diagnosis of membranous glomerulonephritis and 4 had a clinical diagnosis of nephrotic syndrome. A remission was likewise observed in one case each of proved pyelonephritis, suspected lupus erythematosus, and sarcoidosis. In each instance the patients became edema-free and the serum albumin values rose. Hypercholesterolemia, when present, decreased or disappeared at the end of the initial course of therapy, edema when present ultimately cleared in all but 6. Serum albumin values are still below 3.2 gm.% in 8. Hypercholesterolemia, 320 mg. per 100 ml. or higher, is present in 6 patients. The whole blood nonprotein nitrogen was elevated above 40 mg. per 100 ml. in 7 of the 21 patients at the time of the last observation. Creatinine clearances were reduced below 95 ml. per minute in about two thirds of the patients in whom this measurement was available. Hypertension, that is, readings in excess of 142 systolic or 90 diastolic, or both, has persisted or developed in 8 out of 21 patients (Table 2).

TABLE 4.—TABULATION OF HISTOLOGIC DIAGNOSES AND PROBABLE CLINICAL DIAGNOSES IN 54 PATIENTS WITH PROTEINURIA

	Total	*Remission*	*Reduction in Proteinuria*	*No Effect*	*Deaths*
HISTOLOGICAL DIAGNOSIS					
Membranous glomerulonephritis	11	2	4	4	1
Subacute glomerulonephritis	5			1	4
Chronic glomerulonephritis	9		2	3	4
Pyelonephritis	3	1	1		1
Intercapillary glomerulosclerosis	2				2
? Disseminated lupus erythematosus	1	1			
Sarcoidosis	1	1			
Lobular glomerulonephritis	1			1	
Arteriolar nephrosclerosis and diabetes mellitus	1				1
CLINICAL DIAGNOSIS					
Nephrotic syndrome of unestablished etiology	7	4	3		
Chronic glomerulonephritis	11		4	7	
Nephrotic syndrome and diabetes mellitus	1				1
Acute glomerulonephritis	1		1		
TOTAL	54	9	15	16	14

In the 24 patients in group III edema is still present in 12 and the serum albumin below 3.2 gm.% in 16. Cholesterol levels were above 320 mg. per 100 ml. in 11 of the patients at the last measurement. The incidence of azotemia is higher than in group II, occurring in 17 of the patients and ranging from 43 to 331 mg. per 100 ml. Also, creatinine clearances have been found

or during subsequent maintenance in each of these patients. Final nonprotein nitrogen levels were 40 or less when last measured and creatinine clearances were 95 ml. per minute or higher in those in whom this measurement was available. None of them was hypertensive when last seen. In patient J.Hy. in this group, repeat kidney biopsy after 27 days of ACTH therapy demonstrated normal renal tissue in contrast to the changes of membranous glomerulonephritis present at the initial biopsy.

In the 21 patients in whom marked decreases in proteinuria occurred dur-

TABLE 5.—MOST RECENT OR ULTIMATE CLINICAL AND LABORATORY FINDINGS IN PATIENTS IN COMPLETE REMISSION (GROUP I), THOSE WITH MARKED REDUCTION IN PROTEINURIA AT END OF INITIAL COURSE (GROUP II), AND THOSE WHOSE PROTEINURIA WAS BUT SLIGHTLY, IF AT ALL, REDUCED (GROUP III)

Group	No. of patients	Edema (% of pts.)	Hypertension >142 syst. and or >90 diast. (% of pts.)	Serum Albumin <3.2 gm. % (% of pts.)	Serum cholesterol <350 mg./100 ml. (% of pts.)	NPN >40 mg./100 ml. (% of pts.)	Creatinine clearance <95 ml./min. (% of pts.)	Deaths (% of pts.)
I	9	0	0	0	0	0	0	0
II	21	29	38	38	29	33	64	5
III	24	50	54	67	46	71	88	38

to be reduced more often (14 out of 16 patients) but hypertension is only slightly more frequent than in group II. These various manifestations and laboratory findings in the three groups of patients are summarized in Table 5.

B. SIDE EFFECTS OF THERAPY. The appearance of a plethoric moon face and acne, and weight gain were the most frequent concomitant events occurring in all of the patients during the prolonged continuous therapy with these pharmacologic dosages. A buffalo hump and abdominal, trunk or arm striae developed in the majority but not all of the patients. Acne became marked in 4 (E.McG., E.Y., H.R., and I.H.). Slight increases in facial hair were noted in a few female patients on ACTH. Shifting of one of these patients (C.Z.) to steroids was followed by a prompt disappearance of the excessive facial hair. Thinning of scalp hair occurred in one man (M.McC.) and one woman (B.S.) after prolonged maintenance therapy, but in each instance hair growth returned to normal although treatment was continued. Blood pressure readings tended to rise in the majority of patients despite sodium restriction.

During maintenance therapy all of these changes were less pronounced.

C. COMPLICATIONS OR INCIDENTAL UNTOWARD EVENTS DURING THERAPY. In 21 of the 54 patients the initial course of intensive therapy was without incident. During this 4-week period the other 33 patients experienced a total of 39 episodes which might be classified as complications of treatment or as incidental untoward events. These are shown in Table 6.

Among the episodes listed as complications, there were 10 instances of anxiety, confusion or actual psychosis, 7 major infections, and 6 cases of abdominal symptoms and signs, including one patient with acute pancreatitis and one with a bleeding duodenal ulcer. All of these resolved upon withdrawal or completion of therapy. Among the remaining complications one patient developed permanent diabetes mellitus, and thrombophlebitis of the legs appeared in 2 others.

Events believed to have been incidental included pleural effusions, bilateral pneumothorax and coronary insufficiency (Table 6).

In the patients on maintenance therapy for as long as 28 months there were but 8 episodes which were thought to be coincidental events. All of these were mild compared to the events developing during the initial course, and all subsided promptly on interruption or modification of therapy.

D. DEATHS. Four patients died during the initial course of therapy. In 3 of the 4 ACTH had been discontinued: after 21 days in G.W. because of bronchopneumonia, after 7 days in C.C. because of bleeding from a pre-existent duodenal ulcer, and after 7 days in R.S. because of hypertension. Death due to pulmonary edema and bronchopneumonia (G.W.), uremia and bronchopneumonia (C.C.) and cerebrovascular accident (R.S.) occurred 4, 27, and one day, respectively, after treatment was stopped. Pulmonary edema and bronchopneumonia resulted in death of one patient (H.T.) on the 28th day of ACTH treatment (Table 7).

The other 11 patients who died had not been treated within one to 36 months of the date of death. It is noted that the majority of the deaths occurred in patients with known or presumed far-advanced uremia.

E. CHANGES IN SERUM, BLOOD AND URINE SOLUTES. Occasionally temporary rises in nonprotein nitrogen to mildly azotemic levels were noted during the initial course of therapy and quite regularly the fasting blood sugar levels increased. Sporadic minimal glucosuria

TABLE 6.—COMPLICATIONS OR COINCIDENTAL EVENTS OCCURRING DURING INITIAL

TABLE 6.—COMPLICATIONS OR COINCIDENTAL EVENTS OCCURRING DURING INITIAL COURSE OR MAINTENANCE THERAPY

	Initial Course of R		*During Maintenance of* R	
	Patients	*Patients (°)*	*Patients*	*Patients (°)*
None	V.G., C.A., J.K., C.R., J.H., C.Z., J.Ha., M.McC., W.T., S.S., F.B., J.G., J.V., W.C., C.S., D.B., H.L., P.S., R.L., H.H., P.T.	21	E.McG., A.B., J.K., C.Z., J.Ha., R.S., E.Y., S.M., R.S., I.H., G.W., B.M.	12
A. COMPLICATIONS				
CNS				
Anxiety or confusion	R.S., R.S., I.H., J.W., H.P., G.K., M.M., B.M.	8	H.H., C.R., J.V.	3
Psychosis	A.B., D.H.	2		
Convulsion	E.B.	1	S.S.	1
Infections				
Bronchopneumonia	E.B., F.C.	2		
Abscess	J.W., A.B., J.K.	3		
Parotitis	D.B.	1		
Herpes zoster	G.W.	1		
Gastrointestinal				
Pancreatitis	D.B.	1		
Bleeding duodenal ulcer	C.C.	1		
Abdominal pain	S.M., R.S., A.D., J.L.	4		
Endocrine				
Temporary marked hyperglycemia	J.W.	1	M.McM.	1
Diabetes	J.K.	1		
Hyponatremia	A.B.	1		
Menstrual irregularities			B.S.	1
Thyroid enlargement			B.S.	1
Thrombophlebitis	A.W., R.S.	2		
B. COINCIDENTAL EVENTS				
Pleural effusion	H.P., G.P., E.D'A., B.M., A.Y.	5		
Pneumothorax bilateral	F.C.	1		
Pulmonary edema	H.T., G.W.	2		
Coronary insufficiency	D.G.	1		
Cerebral vascular accident	R.S.	1	J.G.	1

was noted in most patients during the intensive therapy but as already indicated, actual diabetes mellitus which persisted was limited to one patient. Also, the usual trends to relative hypochloremia, hypokalemia, and metabolic alkalosis appeared. Only one patient, A.B., developed hyponatremia. The changes in the serum proteins and reduction of creatinine clearance with or without azotemia has developed in one-half or more.

Of the 9 patients whose proteinuria apparently cleared completely and in whom there is at present no clinical nor laboratory evidence of renal or vascular disease, 6 were known or believed to have membranous glomerulo-

TABLE 7.—DATA ON 15 PATIENTS WHO HAVE DIED

Pt.	*Age*	*Dx*	*Type of Death*	*Duration and Dosage* ℞	*Time from Initial* ℞
INITAL HOSPITALIZATION:					
R. S.	31	Chr. G.N.	Cerebral vasc. accident	200 u ACTH 7 days (hypertension)	8 days
G. W.	69	Subac. G.N.	Pulmonary edema; Bronchopneumonia	200 u ACTH 21 days (bronchopneumonia)	25 days
H. T.	56	Pyelonephritis	Pulmonary edema	200 u ACTH 28 days	28 days
C. C.	46	Chr. G.N.	Uremia, duod. ulcer, Bronchopneumonia	200 u ACTH 7 days (bleeding ulcer)	34 days
SUBSEQUENT TO DISCHARGE:					
A. Y.	34	Subac. G.N.	Uremia	200 u ACTH 28 days	14 months
J. K.	54	Neph. Syndrome, diabetes mell.	Uremia, D.M.	200 u ACTH 10 days (carbuncle, D.M.)	17 months
J. G.	32	Membr. G.N.	Cerebral vasc. accident	200 u ACTH 28 days	2 years
G. P.	38	Subac. G. N.	Uremia	100 u ACTH 28 days 200 u ACTH 28 days	27 months
E.D.'A.	19	Chr. G.N.	Uremia	100 u ACTH 28 days	16 months
W.C.	31	Intercap. G. S.	*	200–300 u ACTH 59 days	6 months
				300–500 Cpd. E 38 days	6 months
D. G.	39	Intercap. G. S.	*	200 u ACTH 28 days	12 months+
A. D.	34	Arter. neph., D.M.	*	200 u ACTH 35 days	5 months
G.K.	34	Chr. G.N.	Uremia	200 u ACTH 23 days	3 years
R. L.	42	Subac. G.M., ac. pyelon.	Uremia	50–100 u ACTH 54 days	15 months
J. L.	55	Chr. G.N.	*	500 u ACTH 28 days	13 months

* Died at home.

cholesterol levels have been noted earlier and are shown in Tables 1, 2 and 3.

Discussion. Of the 54 proteinurics treated with ACTH and adrenocortical steroids 4 have been lost to follow-up, 15 have died, and 9 have apparently cleared completely. In the remainder the proteinuria has persisted in varying degrees and impending or manifest renal failure as indicated by marked nephritis or a nephrotic syndrome as a manifestation of glomerulonephritis. These represented about 33% of the patients with either of these two diagnoses. It is noteworthy that not one of the 7 patients known by renal biopsy to have subacute glomerulonephritis or lobular nephritis, none of the 20 others believed to have chronic glomerulonephritis on clinical or histologic grounds, and neither of the 3 with dia-

betes mellitus and proteinuria responded with a complete remission.

Age appears to influence the probability of a remission. Thus in the group of 19 patients with a definite diagnosis of membranous glomerulonephritis or a probable diagnosis of nephrotic syndrome on the basis of glomerulonephritis, the mean age of the 6 who went into remission was 26 years and 2 months in contrast to 33 years and 9 months in those with persistent proteinuria.

The likelihood of a remission can also be gauged in part from the clinical and laboratory responses during or following therapy. Thus persistence of edema, continued hypoalbuminemia, failure of hypercholesterolemia to clear, an elevated nonprotein nitrogen, a diminished creatinine clearance and the persistence or appearance of hypertension argue against an eventual remission. On the other hand the absence of any or all of these changes does not guarantee ultimate disappearance of the proteinuria.

Finally, since definite statements are not justifiable, only speculation about possible deleterious effects of such treatment upon the survival and the course of these patients is possible. None of the deaths resulted from specific toxic reactions such as perforated peptic ulcer and virtually all were of the type usually expected in progressive renal failure, that is, in uremia or following a cerebrovascular accident. Hence, if the therapy is to be implicated in the fatal outcome in these patients, it must be largely ascribed to acceleration of events which ordinarily occur in such patients. Our numbers are too small and controls are not available to permit evaluation of this latter possibility.

At present, in patients with membranous glomerulonephritis, preferably defined by biopsy, the results of therapy probably yield a high rate of remissions than can be expected to occur spontaneously and are sufficiently encouraging to warrant the expense and the potential hazard of therapy. Also it seems worthwhile to treat patients with miscellaneous entities such as disseminated lupus erythematosus, sarcoidosis and pyelonephritis in view of the remissions observed. Such a recommendation cannot be made in chronic or subacute glomerulonephritis nor in those with diabetic nephropathy.

In view of the occurrence of episodes classifiable as major complications of therapy during the initial intensive 4-week treatment and the paucity of such events during maintenance, it would appear desirable to limit treatment to intermittent dosages of ACTH and steroids and to eliminate the initial course of continuous ACTH or steroid administration. There is no evidence at present that this will necessarily decrease the number of remissions.

Summary and Conclusions. 1. Of the 54 patients in the study, 4 have been lost to follow-up, 15 have died in uremia or after a cerebrovascular accident presumed to represent the usual sequence of renal disease, 9 remain completely well, and proteinuria persists in the remainder. In this last group renal failure as indicated by a decreased creatinine clearance or elevated nonprotein nitrogen is present in approximately one-half.

2. Prolonged therapy of proteinuria with pharmacologic dosages of ACTH or adrenocortical steroids was accompanied by complete disappearance of proteinuria in 6 out of 18 patients known or believed to have membranous glomerulonephritis. This did not occur in any of the 26 patients with histologic or clinical evidence of subacute or chronic glomerulonephritis nor in the one patient with lobular glomerulonephritis.

3. Complete remissions were noted in one instance each of proteinuria with a histologic diagnosis of renal sarcoidosis, one of possible disseminated lupus, and in one out of 3 cases of pyelonephritis.

4. Neither of 2 patients with intercapillary glomerulosclerosis responded; this was also true in one instance of proved nephrosclerosis and diabetes mellitus and in one case of presumed acute glomerulonephritis.

5. Most of the usual side effects of prolonged pharmacologic dosages of ACTH or adrenocortical steroids were observed in each patient during the initial course and much less frequently or to a lesser degree during subsequent maintenance therapy.

6. Toxic reactions attributable to or occurring incidentally during treatment occurred during the initial course in more than one-half of the patients. Anxiety, confusion, or psychosis was the leading manifestation, developing in a total of 10 patients. Infections were next in order, involving 7 patients. Abdominal complications, only 2 of which were definitely diagnosed, one case each of pancreatitis and of bleeding duodenal ulcer, appeared in 6 patients. Thrombophlebitis appeared in 2 others. Only one patient developed permanent diabetes. Such complications were much less frequent and milder during intermittent maintenance therapy. A number of events such as pleural effusions, pneumothorax, and others were believed to be coincidental.

7. Though conclusive evidence that these remissions were induced by therapy or that the remissions represented disappearance of the underlying lesion is lacking, treatment of instances of membranous but not of subacute or chronic glomerulonephritis seems worthwhile in view of the gravity of the renal afflictions. The high incidence of serious toxic reactions during 4 weeks of intensive therapy and the much greater safety of intermittent therapy indicates that treatment should be limited to the latter.

REFERENCES

1. **Burke, E. C.:** Proc. Staff Meet., Mayo Clin., **33**, 12, 1958.
2. **Danowski, T. S., Greenman, L., Mateer, F. M., Parsons, W. B., Weigand, F. A., Mermelstein, H.,** and **Peters, J. H.:** J. Clin. Invest., **30**, 984, 1951.
3. **Danowski, T. S., Weigand, F. A., Greenman, L., Gailani, S., Greenberg, W. V.,** and **Mateer, F. M.:** A.M.A. Am. J. Dis. Child., **93**, 604, 1957.
4. **Galán, E.,** and **Maso, C.:** Pediatrics, **20**, 610, 1957.
5. **Greenman, L.,** and **Danowski, T. S.:** Pennsylvania Med. J., **55**, 563, 1952.
6. Iidem: J. Clin. Invest., **33**, 938, 1954.
7. **Greenman, L., Weigand, F. A.,** and **Danowski, T. S.:** A.M.A. Am. J. Dis. Child., **89**, 169, 1955.
8. **Lange, K., Strang, R., Slobody, L. B.,** and **Wenk, E. J.:** A.M.A. Arch. Int. Med., **99**, 760, 1957.
9. **Mateer, F. M., Erhard, L. H., Price, M., Weigand, F. A., Peters, J. H., Danowski, T. S., Tarail, R.,** and **Greenman, L.:** J. Clin. Invest., **30**, 1018, 1951.
10. **Mateer, F. M., Weigand, F. A., Greenman, L., Weber, C. J., Jr., Kunkel, G. A.,** and **Danowski, T. S.:** A.M.A. Am. J. Dis. Child., **93**, 591, 1957.
11. **Parrish, A. E., Watt, M. F.,** and **Howe, J. S.:** A.M.A. Arch. Int. Med., **100**, 620, 1957.
12. **Riley, C. M., Davis, R. A., Fertig, J. W.,** and **Berger, A. P.:** J. Chronic Dis., **3**, 640, 1956.
13. **Roscoe, M. H.:** Quart. J. Med., **25**, 353, 1956.

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USE OF BUCCAL TRYPSIN IN TWO DIABETICS WITH THE NEPHROTIC SYNDROME: A PRELIMINARY REPORT

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Over a period of a year and a half, buccal trypsin has been used in the medical renal clinic of a large municipal hospital. The project is designed to evaluate the effect of this proteolytic and anti-inflammatory enzyme in chronic renal infections which do not respond to combinations of antibiotics. In our experience, nearly all cases of chronic renal failure seem to develop secondary infections. Many do not respond to antibiotics either singly or in combination, even though the causative organisms may be susceptible *in vitro*.

Twelve patients have been treated to date for periods up to 9 months. Among these were 2 diabetics with nephrotic syndrome in whom the changes were quite remarkable. It is the purpose of this preliminary paper to outline the clinical and laboratory improvements which occurred and to suggest evaluation of buccal trypsin as a potential therapeutic agent in this entity.

In theory, trypsin could bring about an alteration in cellular permeabilities so that antibiotics might act more effectively in inaccessible areas of kidney tissue. When it was found that trypsin could be absorbed through the membranes of the mouth, trial on an outpatient basis became feasible. To date results have been encouraging. Actual clearing of infection and alteration of flora have occurred in certain patients whose patterns of infection had been constant over many months.

BACKGROUND. The information which led to the trial in patients with renal infection is reviewed. Experimentally trypsin has been shown to prevent and reverse the edematous changes of inflammatory reactions (Beiler, Brendel and Martin[2,8], Moss *et al.*[10]). The effect of the enzyme cannot be classed as anti-inflammatory in the sense of the adrenal corticoids, however, because it does not block granulation tissue formation (Adamkiewicz, Rice and McColl[1], Kleinfield and Habif[5]).

If trypsin does not block inflammation *in toto* but does prevent the accumulation of soft tissue edema, it is reasonable to assume that it acts either directly or indirectly on the factors which prevent dispersal of fluids. Martin[7] discusses the reasons for believing the effect is due to a direct depolymerizing action of trypsin, while Innerfield, Schwarz and Angrist[4], and Moser[9] present different theories of indirect action.

Clinical work substantiates the lab-

oratory data. The status of trypsin therapy was reviewed by Moser[9], and an extensive use in trauma was reported by Lichtman[6]. The effect on fluid accumulations, however, is not limited to serum factors, Silbert[12] showing mobilization of inspissated mucus in patients with upper respiratory diseases. And finally, most pertinent to this work were the observations of Innerfield, Angrist, Schwarz and Ruggiero[3] that persistent *Proteus vulgaris* infections of the urinary tract, not responsive to antibiotics, did respond when intravenous trypsin was given. Rapoport, Herzfeld and Lavon[11] recently confirmed these findings using the intramuscular route.

Case Reports. CASE 1. R.M. This 33-year-old white man has been followed in the medical renal clinic since April 24, 1956. He is a known diabetic of 20 years' duration and has been reasonably controlled with a mixture of protamine zinc and regular insulin, totaling about 50 U daily. Early in his disease he gave a history of being quite brittle, but during the past several years there have been no episodes of shock or coma.

The chief complaint for which he was referred to the renal clinic was puffiness of the face, hands, and ankles. This had an insidious onset about 4 months previously. Prior to the incipient swelling, he states that he was told by his famly doctor that he had pneumonia and was given penicillin. Associated with the swelling, he noted pallor and fatigue but was able to continue to work.

Physical examination on his first visit revealed marked pallor, the face puffy, especially about the eyes, fingers swollen, and a 1+ ankle edema. The blood pressure was 140/80, pulse, 90, respiration, 20. The chest was clear and the heart was moderately enlarged. Eye ground consultation indicated Grade II diabetic retinopathy. The abdomen was soft and nontender.

The impression was Kimmelstiel-Wilson's disease. Laboratory studies tended to confirm this diagnosis. The intravenous pyelogram, done prior to his referral May 1, 1956, showed normal function and structure. Twenty-four hour urine protein was 12.5 gm. Routine urines showed a concentration up to 1.027 with between 2 and 4+ albuminuria. Microscopic examination repeatedly showed between 15 to 80 red blood cells, 5 to 10 leukocytes and variable amounts of casts. Hemoglobin, on repeated occasions between May 1, 1956, and February 5, 1957, was between 11 and 13 gm. per 100 ml. Repeated urine cultures were positive for *Streptococcus gamma*, *Neisseria catarrhalis* and *M. pyogenes albus*, coagulation negative. The serum cholesterol ranged from 336 mg. per 100 ml. with 56% esters to 422 mg. per 100 ml. with 75% esters. Total proteins were between 5.5 gm. per 100 ml. with a ratio of 3.5:2 to 7.1 gm. with 5.3:1.8 by January 26, 1957. Serum electrolytes were essentially normal except for a CO_2 of 18 mm. per L. Between January 12, 1955, and December 13, 1956, diabetic retinopathy progressed from Grade I to Grade II.

Initially treatment consisted of salt restriction and diabetic diet. The edema did not subside but varied in amount. Because of his work and lassitude about his condition his visits were not regular and at times infrequent. His weight fluctuated around 147 pounds in accordance with the edema, there never being more than a 4-pound deviation from the mean. On September 4, 1956, the patient was seen with a paronychia of the toe and was hospitalized for treatment. He responded well to antibiotics. On September 6, 1956, a needle biopsy of the kidney was performed with a Vim Silverman needle. This yielded a 1.5 cm. strip of tan tissue which microscopically showed diabetic glomerulosclerosis.

Because of a gradual downhill course, it was decided to begin the patient on subcutaneous heparin. Laboratory studies were repeated as a baseline on October 2, 1956. The electrophoretic pattern showed: Albumin, 1.94; α_1 globulin, 0.45; α_2 globulin, 1.31; β globulin, 0.43; γ globulin, 0.85; total protein, 5.5. Serum electrolytes were normal. There was no change in the urine or blood count. The urine culture remained positive. Twenty-four hour total protein excretion was 12 gm.

On October 23, 1956, the serum cholesterol was 422 mg. per 100 ml. with 53% esters. Heparin 100 mg., every other day, was administered for 3 weeks and appeared to bring about some edema loss. The heparin dosage was then reduced to 100 mg., 2 times weekly and the patient increased his activity. By December 11, 1956, there was increased swelling of the ankles following extensive exercise. This was combined with marked fatigue. The patient was again urged to restrict his activities.

In general, there had been no change clinically by February 5, 1957, after 15 weeks of heparin treatment, but the albumin on the electrophoretic curve had risen from 1.94 at the start of the heparin treatment, to 2.53 after 15 weeks. On January 8, 1957, the serum cholesterol was 349 mg. per 100 ml. with 75% esters.

Because of a recent head cold and persistent positive urine cultures it was decided to add buccal trypsin to the therapy. This was attempted February 5, 1957, but the patient complained of burning and took very little until February 27, 1957, when he was again instructed as to the proper use. It was not until March 12, 1957, that the patient actually began taking 6 to 10 tablets daily, on a 2-hour schedule while awake. Since no clinical improvement had occurred, heparin was stopped and the only therapy was intensive buccal trypsin.

The patient continued to be lax about his clinic visits for the next 8 weeks. Studies performed on April 9, 1957, showed a cholesterol of 403 mg. per 100 ml., and total proteins 6.8 gm. with A/G ratio 4.4:2.4. At this point the urine culture was found to be negative. Although the weight did not change significantly, the patient stated that he felt somewhat better and the edema was less but still present. By May 7, 1957, the blood urea nitrogen was 26 mg. per 100 ml.; the hemoglobin and blood count were normal but the cholesterol was now 243 mg. per 100 ml. with 59% esters. At this point he claimed that he felt much better and no edema was apparent.

Since then the patient has improved remarkably and volunteers the information that he feels better than he has in years. There has been no recurrence of the edema except on one occasion when he was out of buccal trypsin for the period of one week.

Laboratory data tended to coincide with the clinical improvement. By July 9, 1957, the cholesterol was 234 mg. per 100 ml. with 55% esters. Urine cultures remained negative. On July 9, 1957, total 24-hour urine protein was 9.1 gm. The hemoglobin was 14.3 gm. per 100 ml. Urines did not change except for less microscopic hematuria excepting one specimen on July 9 which was loaded with casts. These, however, did not persist. Phenolsulfonphthalein excretion was 16, 16, 12 and 12% at 15, 30, 60 and 120 minutes. Besides the reduction in cholesterol and esters, it is interesting that the electrophoretic pattern of July 18, 1957, showed a significant lowering of alpha 2 globulin from 1.27 to 1.11. Albumin remained unchanged as did total protein.

Seen October 21, 1957, the patient was completely asymptomatic, working full time

	Control *10–2–56*	*After 15 weeks Heparin* *2–5–57*	*After 4 months Trypsin* *7–18–57*
Albumin	1.94	2.53	2.54
Alpha$_1$ globulin	.45	.37	.47
Alpha$_2$ globulin	1.31	1.27	1.11
Beta globulin	.43 (Beta$_2$.52)	.95	.97
Gamma globulin	.85	.89	1.00
Total protein	5.5	6.0	6.1

Normal value

3.52–4.72 Albumin
0.16–0.44 Alpha$_1$ globulin
0.32–0.76 Alpha$_2$ globulin
0.45–0.93 Beta globulin
0.97–1.73 Gamma globulin

1-19-56 Diabetic retinopathy
1-26-56 *Strep. gamma, Neisseria catarrhalis*
4-26-56 Cult. urine, *Micro. pyogenes albus*, cog. reg.
5- 1-56 Normal I.V.P.
12-13-56 Eye grounds, grade II, diabetic retinopathy

B.P.: 140/80
Wt. 12-11-56—150
2-5-57—144½
10-15-57—141

without fatigue and displaying no edema. Again he stated that he felt quite healthy and normal. The only therapy has been buccal trypsin.

This patient is unavailable for follow-up laboratory studies because of his unwillingness to take time off from a full-time job.

CASE 2. G.B. This 55-year-old white woman was first seen in the renal clinic May 15, 1956, being referred because of edema, albuminuria and puffiness. She is a known diabetic who has been controlled with diet alone for the 8-year history of her disease. The pertinent findings from various clinics were mild osteoarthritis, urethrocele repair in 1953, and recent menopausal syndrome treated in the endocrine clinic with estrogen therapy. Her chief complaints were frequency, nocturia and dysuria which have occurred intermittently in the past. She could not relate a specific date for the onset of the mild swelling.

Physical examination showed pallor and a suggestion of edema of the face, hands, and ankles. Her blood pressure was 120/80. The heart was slightly enlarged to the left, as the border percussed 1 cm. lateral to the mediоclavicular line in the 5th intercostal space. The lungs were clear. The abdomen was soft and nontender.

Baseline laboratory work from multiple studies between the first visit and institution of buccal trypsin April 16, 1957: Urines with trace to 1+ protein, persistent concentration to 1.020, occasional glycosuria, pyuria, and occasional hematuria. The hemoglobin ranged 11 to 13 gm. and there was a normal differential count of the leukocytes. The serum Na was in the range of 134 to 140, K 3.4 to 3.7 mEq. per L., CO_2 22 to 27 mm. per L., Cl 97 to 100 mEq. per L., blood urea nitrogen 16 to 20 mg. per 100 ml. Ten successive urine cultures were positive for alpha *Staph. B. subtilis* and *M. pyogenes*. On May 29, 1956, the serum calcium was 9.1 mg. per 100 ml., phosphate 3.5 mg., the alkaline phosphatase 1.4 units, and the serum cholesterol 493 mg. per 100 ml.

Her initial outpatient course was difficult. Burning and dysuria became severe. By May 29, 1956, in view of 2 urines with microscopic pyuria and positive cultures, she was begun on a course of Gantrisin. Because of an hypersensitivity response this was discontinued after 8 tablets. Her face, hands, and ankles became puffy and she developed ascites. There was an increase in weight from 144 to 146½ lb. On June 12, 1956, she was begun on a course of tetracycline which was continued until June 29, 1956, without any improvement. Puffiness progressed to the point that she could no longer wear her rings. Rigid salt restriction along with erythromycin was instituted for the next 2 weeks. This did not improve the situation. Intravenous urogram showed good function and a possible cyst of the right kidney. Chest roentgenogram showed slight cardiac enlargement and electrocardiogram showed abnormality in the T waves involving the left ventricle. A barium enema was negative. All medication was withdrawn and by August 28, 1956, swelling was less but soon increased again. In September, erythromycin was again given for several days without effect and then Furadantin was begun 100 mg. 4 times a day for 6 days. A marked allergic reaction with urticaria resulted. This was treated with Pyribenzamine. Later in November the patient developed a large abdominal wall abscess and was treated with incision and drainage with local radiation.

The patient continued with positive urine cultures, burning, and a gradual increase in the generalized edema in spite of all antibiotics and dietary therapy. Her condition seemed to deteriorate gradually but the laboratory findings remained unchanged. By March 19, 1957, the patient had marked edema and severe burning of the soles of the feet. Urine then showed innumerable leukocytes and persistent infection. Cathosulfa was then begun and continued until March 30, 1957. There was some lessening of the edema and questionable improvement. By April 16, 1957, her condition had again deteriorated. A urine culture on April 2, 1957, yielded alpha streptococci.

Because of her clinical picture and persistent infection, she was begun on buccal trypsin 2.5 mg., 4 times a day. At this time her phenolsulfonphthalein excretion was 20–15–15% per hr. All antibiotics were stopped. It was not learned until her next visit that on April 16 she had obtained her first negative urine culture which, however, was of short duration as the culture was again positive on the next 2 visits with the patient receiving only buccal trypsin.

Little improvement occurred by May 14, 1957, the cholesterol was 437 mg. per 100 ml. and the total protein 7.3 gm. with the A/G ratio 5.1:2.2. Leukocytes and hemoglobin remained unchanged and microscopic pyuria persisted. However, by May 28, 1957, the urine culture had become negative and the patient had only intermittent edema and had a sense of well being. Since that time she has had intermittent puffiness of the face and hands but a complete disappearance of

ascites. By August 20, the cholesterol was 331 mg. per 100 ml., the total protein 6.6 with an A/G ratio 4.5:2.3, and the patient stated that she felt better than she had in quite some time. More recent studies have indicated a continuing negative urine culture and a diminution in pyuria since June with the exception of September 17 when *B. subtilis* was recovered in a voided specimen; this probably was a contaminant because all subsequent catheterized urine cultures were negative.

The most recent studies indicate, as of November, 1957: urine, specific gravity 1.028; protein negative; sugar ++; red blood cells 3 to 5; leukocytes 2 to 4; blood sugar 126 mg. per 100 ml.; cholesterols between 331 and 391; total protein 8.1 gm. with 5.1 gm. albumin; serum Na, 125; K, 4.2; CO_2, 22; and chloride, 91. The phenolsulfonphthalein excretion in the first 20 minutes increased from 25% to 45%, over a period of one year, suggesting a beneficial effect on renal blood flow; the total excretion, however, probably did not change significantly. It is now 95%. In the absence of the third specimen in 1956, the excretion was 70%. The eye examination revealed grade I diabetic retinopathy along with grade I sclerotic changes.

Clinically, this patient has progressed satisfactorily and no further therapy has been added. Total time of administration of buccal trypsin (now up to 30 mg.) has been 8 months.

She is now on unlimited activity. Recent blood and electrolyte studies have been normal excepting a fluctuating cholesterol showing a tendency to rise. The patient clinically remains edema free and in good condition without other medication.

Discussion. In the cases reported here, it is of interest that the patients state that they feel better than they have in years. This is to some extent verified by laboratory studies. Reduction in cholesterol and assumed phospholipids, as well as certain changes in total protein and electrophoretic patterns, are unusual in our experience with such diabetics.

The nephrotic syndrome in these patients may have been enhanced by secondary renal infection. Case 1 had a kidney biopsy showing Kimmelstiel-Wilson findings. Case 2 presents clinical and laboratory data for this syndrome but the biopsy was more compatible with chronic glomerulonephritis or lipid nephrosis.

Why these diabetics who lack pancreatic enzyme should be benefited by the addition of a single exogenous enzyme makes interesting speculation. Due to the outpatient basis of these patients and the only occasional check of blood sugars, no data are presently available on changes which may have occurred in the insulin requirements. Such changes if present would only be confusing, however, because of the well known decreases of insulin requirement with progressive renal failure (Zubrod, Eversole and Danna[13]).

Placebo effects were given little weight as these 2 patients had received many types of therapy prior to administration of trypsin. They were always informed as to the drug administered but were not told of any potential pharmacology. A rapid response was not elicited, either clinically or by laboratory test but, after several months, both cases volunteered that they felt better than they had in years.

The chemical changes found would indeed parallel those of spontaneous diuresis or cure of the nephrotic syndrome; however, considering the permanent vascular alterations, the probability of a spontaneous remission is low. That these 2 cases in all aspects showed similar amelioration which was progressive with continuing treatment is, in our opinion, of some importance. Observations of diabetics with renal involvement along with the further study of the effect in renal infection are the subjects of long range investigations with buccal trypsin.

SIDE EFFECTS AND TOXICITY. Toxicity to buccally administered trypsin has been practically negligible. Both patients have taken between four and twelve 2.5 mg. tablets daily for periods over 9 months. Using the buccal route,

it thus has been possible to administer easily 30 mg. of trypsin or its derivative across the membrane daily. The prolonged period of administration may play an important role. A soft tablet recently made available has proven less irritating and more acceptable to these patients, and also to those in the longer study.

The action of this drug, in our mind, bears investigation not only in diabetics with the nephrotic syndrome where renal infections may be superimposed, but also in diabetics wherever there may be other resistant infections. At this point, one could not even hypothesize as to why such responses occurred in the nephrosis of diabetes in the 2 cases reported. Perhaps there were 2 spontaneous remissions, but one of the authors who has specialized in diabetes and another who has treated many cases of nephrosis feel that this is more than coincidence and, therefore, believe this observation worthy of reporting at this early date.

Summary. Large doses of buccal trypsin (30 mg. daily) may be safely administered over a period of months without significant toxicity. Two diabetics with the nephrotic syndrome experienced marked clinical and laboratory improvement with the administration of buccal trypsin in large doses over a prolonged period. The clearance of infection may play a role. Primary insulin deficiency in the diabetic and the addition of a pancreatic enzyme provokes speculation. To date we feel much more study is warranted both in renal infection and in the entire infected nephrotic stage of renal failure.

ACKNOWLEDGMENT: Grateful acknowledgment is made to the Clinical Research Department, The National Drug Company, for making available the tablets used in this investigation.

REFERENCES

1. **Adamkiewicz, V. W., Rice, W. B.,** and **McColl, J. D.**: Canad. J. Biochem. & Physiol., **33**, 332, 1955.
2. **Beiler, J. M., Brendel, R.,** and **Martin, G. J.**: Proc. Soc. Exper. Biol. & Med., **89**, 274, 1955.
3. **Innerfield, I., Angrist, A., Schwarz, A.,** and **Ruggiero, W.**: Surg. Forum, 1952 Clinical Congress, Am. Coll. Surg. Philadelphia: W. B. Saunders Co., p. 526, 1953.
4. **Innerfield, I., Schwarz, A. W.,** and **Angrist, A. A.**: J. Clin. Invest., **31**, 1049, 1952.
5. **Kleinfield, G.,** and **Habif, D. V.**: Proc. Soc. Exper. Biol. & Med., **87**, 585, 1954.
6. **Lichtman, A. L.**: Internat. Rec. Med., **170**, 322, 1957.
7. **Martin, G. J.**: Exper. Med. & Surg., **13**, 156, 1955.
8. **Martin, G. J., Brendel, R.,** and **Beiler, J. M.**: Arch. Internat. Pharm. et Therap., **96**, 124, 1953.
9. **Moser, K. M.**: New England J. Med., **256**, 258 and 303, 1957.
10. **Moss, J. N., Brendel, R., Simon, H., Beiler, J. M.,** and **Martin, G. J.**: Arch. Internat. Pharm. et Therap., **110**, 375, 1957.
11. **Rapoport, C. H., Herzfeld, I.,** and **Lavon, E.**: Acta Med. Orient, **15**, 55, 1956.
12. **Silbert, N. E.**: Dis. Chest, **29**, 520, 1956.
13. **Zubrod, C. G., Eversole, S. L.,** and **Danna, G. W.**: New England J. Med., **245**, 518, 1951.

(Interlingua on page 574)

SUMMARIO IN INTERLINGUA

(See page 545 for original article)

Therapia A ACTH O Steroide Adrenocortical Pro Proteinuria In Adolescentes E Adultos

1. Ex le 54 patientes in iste studio, 4 esseva perdite al observation ulterior, 15 moriva in uremia o post accidentes cerebrovascular que representava pre-

sumitemente le sequentia usual de morbo renal, 9 remane completemente ben, e proteinuria persiste in le alteres. In iste ultime gruppo, insufficientia renal—evidente per un reduction del clearance de creatinina o per elevate concentrationes de nitrogeno nonproteinic—es presente in approximativemente un medietate.

2. Le prolongate therapia de proteinuria con dosages pharmacologic de ACTH o de steroides adrenocortical esseva accompaniate del disparition complete de proteinuria in 6 ex 18 patientes con establite o presumite glomerulonephritis membranose. Isto non occurreva in ulle del 26 patientes con provas histologic o clinic de glomerulonephritis subacute o chronic e etiam non in un patiente con glomerulonephritis lobular.

3. Remissiones complete de proteinuria esseva notate in un caso con un diagnose histologic de sarcoidosis renal, un caso de possibile lupus disseminate, e in un ex 3 casos de pyelonephritis.

4. Ni le un ni le altere de 2 patientes con glomerulosclerosis intercapillar respondeva positivemente al therapia. Le mesmo esseva ver in un caso de establite nephrosclerosis e diabete e in un caso presumptive de glomerulonephritis acute.

5. Le majoritate del usual effectos lateral de prolongate cursos de dosages pharmacologic de ACTH o de steroides adrenocortical esseva observate in omne le patientes durante le periodo initial e multo minus frequentemente o a grados minus marcate durante le subsequente therapia de mantenentia.

6. Reactiones toxic attribuibile al therapia o occurrente incidentalmente durante illo esseva constatate in le periodo initial in plus que un medietate del patientes. Anxietate, confusion, o psychose esseva le manifestationes le plus frequente e se trovava in un total de 10 patientes. Infectiones sequeva in le ordine de frequentia e afficeva 7 patientes. Complicationes abdominal appareva in 6 patientes, sed solmente 2 de iste casos esseva diagnosticate definitemente, le un como pancreatitis e le altere como sanguination de ulcere duodenal. Thrombophlebitis occurreva in 2 altere patientes. Un sol patiente disveloppava diabete permanente. Tal complicationes esseva multo minus frequente e plus leve durante le therapia intermittente de mantenentia. Un numero de evenimentos—effusiones pleural, pneumothorace, e alteres—esseva interpretate como coincidentias.

7. Ben que il non existe provas conclusive que iste remissiones esseva inducite per le therapia o que le remissiones representava un disparition del lesion subjacente, le tractamento de casos de glomerulonephritis membranose (sed non de glomerulonephritis subacute o chronic) pare valer le pena in vista del gravitate del afflictiones renal. Le alte incidentia de serie reactiones toxic durante 4 septimanas de therapia intense e le multo plus grande indemnitate del therapia intermittente indica que le tractamento deberea esser restringite al secunde.

ELECTROPHORETIC STUDIES OF SERUM PROTEINS IN HEMOCHROMATOSIS*

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Idiopathic hemochromatosis is characterized by increased iron absorption with excessive deposition of hemosiderin in the liver, pancreas, adrenal glands, heart, and other tissues (Finch and Finch[10]). Cirrhosis of the liver and diabetes mellitus are among the characteristic complications of the disease. Thus, serum protein changes similar to those observed in liver disease and diabetes mellitus would be anticipated in cases of hemochromatosis which have these complications. Such protein changes have been reported in a small number of cases studied electrophoretically (Bodard, Osinski and Stein[3], Cagli, Napolitano and Scuro[5], Gray and Guzman Barron[13], Koenig, Weiger and Sowinski[19], Poli *et al.*[31]), but there is a lack of evidence in regard to alterations in uncomplicated cases of hemochromatosis.

The present study has shown that in relatively advanced cases the serum protein changes are similar to those observed in liver cirrhosis and diabetes, and that significant alterations occur even in cases in which there is no clinical evidence of such complications.

Materials and Methods. Seventeen patients with idiopathic hemochromatosis were studied. A summary of the important clinical and laboratory data for these patients is presented in Table 1. Pigmentary cirrhosis was demonstrated in all patients by means of liver biopsy, but 4 (cases 1, 9, 15, 16) had normal or only slightly impaired liver function and were without diabetes. Two other patients (cases 6 and 11) had excellent liver function, but did have definite diabetes mellitus. Blood samples were obtained by venipuncture without anticoagulant; the serum was promptly separated and analyzed. The Klett-Tiselius electrophoresis apparatus with an 11.0 ml. analytical cell and diethylbarbiturate buffer of pH 8.6 and ionic strength 0.1 were used. The serum proteins, diluted with 3 volumes of buffer and dialyzed against 2 liters of buffer for 24 hours at 1.2° C., were allowed to migrate for 150 minutes in 1.2° C. under the influence of a potential gradient of 7.5 volt cm.$^{-1}$. The patterns were recorded by the Schlieren scanning technique of Longsworth[21]. Electrophoretic components were calculated as absolute concentrations by fourfold enlargement, tracing, and planimetry of the patterns by the method of Longsworth[22] using the specific refractive index of human serum proteins given by Perlmann and Longsworth[30]. Sera from 20 normal subjects and from 2 patients with transfusion hemochromatosis (hypoplastic anemia) were analyzed under identical conditions.

The distribution of each component was checked for normality by the criteria of skew-

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TABLE 1.—CLINICAL AND LABORATORY STUDIES ON PATIENTS WITH HEMOCHROMATOSIS

Patient No.	*Age*	*Sex*	*BSP Retention %*	*Total Bilirubin mg./100 ml.*	*Alkaline Phosphatase B.U.*	*Thymol Units*	*Cephalin Flocc.*	*Diabetes**	*Insulin U/Day*	*Hepatomegaly*	*Spider Angiomata*	*Palmar Erythema*	*Splenomegaly*	*Body Hair*	*Testicular Atrophy*
1	44	M	2.5	0.57	1.2	3.0	0	0	0	+	0	0	+	Normal	0
2	60	M	9.0	—	—	1.4	1+	+	70	+	+	0	0	Scanty	+
3	56	M	0.0	0.79	4.7	48.0	0	+	60	+	+	+	0	Absent	+
4	59	M	12.0	0.4	3.6	23.0	—	+	0	+	+	+	+	Scanty	0
5	62	M	—	2.76	4.1	8.0	—	+	15	+	+	+	0	Scanty	+
6	58	M	—	0.4	4.0	4.2	3+	+	10	+	0	0	0	Normal	±
7	53	M	10.0	0.4	2.3	1.5	2+	+	0	+	+	+	0	Scanty	+
8	54	F	32.0	0.83	5.2	36.0	—	+	85	+	+	+	0	Normal	—
9	42	M	0.0	0.4	—	5.0	1+	0	0	+	0	0	0	Normal	0
10	65	M	26.0	1.6	—	—	4+	+	60	+	+	+	+	Normal	+
11	60	F	5.0	0.45	5.2	1.7	—	+	90	+	0	0	0	Normal	—
12	52	M	11.0	0.97	6.2	26.0	—	+	40	+	+	+	+	Scanty	±
13	62	M	12.0	0.35	10.7	24.0	—	+	25	+	+	+	+	Scanty	+
14	40	M	42.0	1.36	11.0	18.8	4+	0	0	+	+	+	+	Scanty	0
15	29	M	1.0	0.72	8.2	7.2	3+	0	0	+	0	+	+	Normal	0
16	49	M	1.3	0.46	5.9	2.0	1+	0	0	+	+	0	+	Scanty	±
17	67	M	13.0	0.86	4.4	4.4	3+	+	40	+	+	0	0	Scanty	+

*Based on either elevated fasting blood sugar or diabetic glucose tolerance curve.

ness and kurtosis (Snedecor[39]). Mean values and standard deviations were computed for the normally distributed components. For the α_2-globulin in hemochromatosis, which was found to be log-normally distributed, the median and the range (computed from the mean log plus or minus 2 logarithmic standard deviations) were calculated. Values obtained for patients with hemochromatosis were compared to the normal values by testing first for homogeneity of variance (Snedecor[39]) and then applying the Student's t test when the variances were found to be homogeneous or the Cochran-Cox test (Snedecor[39]) in the cases of unequal variances. The existence of correlations among the electrophoretic components and other clinical data was tested for by multiple regression analysis (Walker and Lev[42]).

Results. The serum electrophoretic patterns of the 17 cases of idiopathic hemochromatosis and one from the normal control group, which were identically processed, are shown in Fig. 1. Values for total serum protein, of each of the electrophoretic components, and of the albumin:globulin (A/G) ratio are tabulated in Table 2. The application of the criteria for skewness and kurtosis indicated that the idiopathic hemochromatosis data could be considered normally distributed ($P > 0.05$) with the exception of the α_2-globulin which was not normally distributed but followed a log-normal distribution ($P > 0.05$). The histograms and probability lines in Fig. 2 illustrate these points. The mean values and standard deviations of the normally distributed data and the median and range of the α_2-globulin are recorded in Table 2. Appropriate statistical comparison with the normal values revealed that in idiopathic hemochromatosis neither the mean nor the variance of the total protein differs significantly from normal ($P > 0.05$). The variance was found to be significantly higher ($P < 0.01$) than normal in the β- and γ-globulins. Significantly lower than normal mean values were found in the albumin ($P < 0.05$), and particularly in the α_1-globulin ($P < 0.01$). There is an elevation of the mean of the γ-globulin of borderline significance ($P \sim 0.05$), but the mean of the β-globulin appears to be normal. The log-normal distribution of the α_2-globulin in the cases of idiopathic hemochromatosis renders unfeasible its comparison to that component in the normal serum, which is normally distributed. However, a simple inspection indicates that the median values of the α_2-globulin are somewhat higher than the normal mean and a considerable number of cases fall well above the normal range. The lower albumin and the higher α_2- and γ-globulins result in significantly lower A/G ratio ($P < 0.05$). Figure 2 provides a visual comparison of the data from the cases of idiopathic hemochromatosis with those from the normal sera. The overlapping of the bell-shaped probability curves is least in the α_1-globulin and almost complete in the case of the total protein. A multiple regression analysis, designed to bring out any correlations that might exist among the various electrophoretic components and the severity of liver involvement or diabetes mellitus, failed to show any dependency of the serum proteins on the degree of such complications. However, it revealed that a positive correlation exists between the β- and γ-globulins (correlation coefficient $r = 0.53$) and a negative correlation between: (a) the albumin and the γ-globulin ($r = 0.71$), (b) the albumin and the β-globulin ($r = 0.47$), and (c) the albumin and the combined β- and γ-globulins ($r = 0.70$).

The data for the 2 cases of transfusion hemochromatosis fall within normal limits with the possible exception of the γ-globulin in case 18 which appears to be just below the normal range.

Discussion. Serum protein alterations

in hemochromatosis have been reported by several authors who used various chemical methods (Althausen *et al.*[1], Deardorff and Kuhl[6], Marble and Cabell Bailey[23]). Electrophoretic studies have been reported by Gray[13], Poli[31], Koenig[19] (each of whom studied a single case), Bodard[3] (who studied 4 cases of idiopathic and one of transfusion hemochromatosis), and Cagli[5].

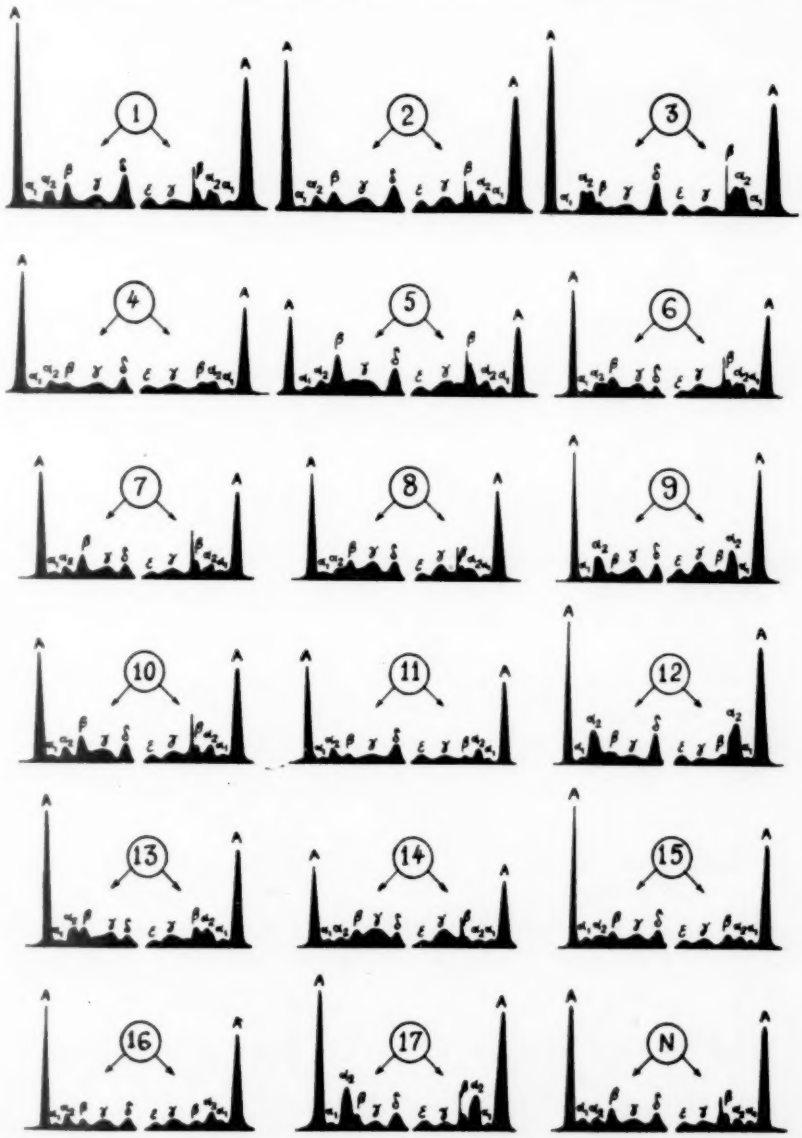

Fig. 1.—Electrophoretic patterns of serum proteins after migration for 150 minutes in diethylbarbiturate buffer, pH 8.6, ionic strength 0.1, under the influence of a potential gradient of 7.5 volt cm.$^{-1}$, at 1.2° C. Patterns 1 to 17 are for idiopathic hemochromatosis; pattern N is a normal control.

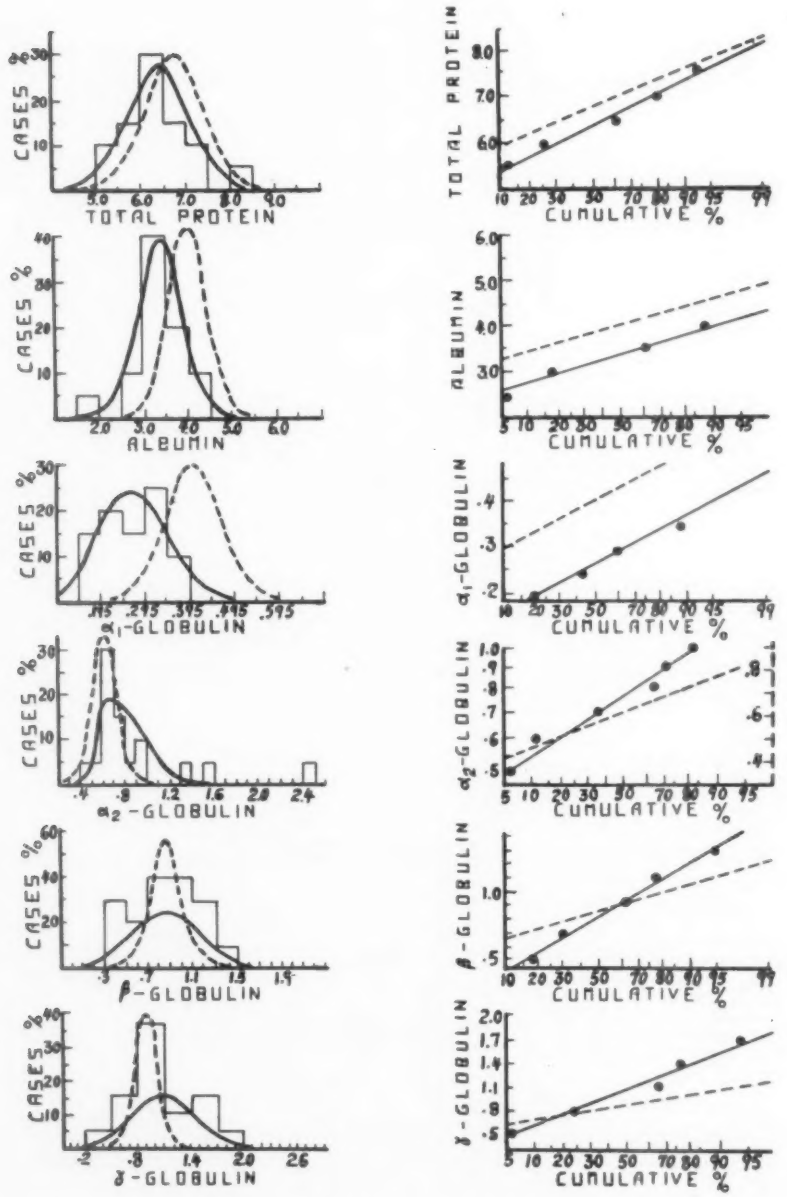

Fig. 2.—Distribution of serum proteins in idiopathic hemochromatosis expressed as gm. per 100 ml. of serum. Solid lines are idiopathic hemochromatosis; broken lines are normal values.

The observed changes resemble those found ... ver cirrhosis, and it has been suggested that they simply reflect the liver involvement (Althausen *et al.*[1], Bodard, Osinski and Stein[3], Deardorff and Kuhl[6], Koenig, Weiger and Sowinski[19], Marble and Cabell amount of α_1-globulin. Even the 4 cases which showed neither significant impairment of liver function nor diabetes had α_1-globulin levels either below normal (cases 1 and 9) or at the lower limit of the normal range (cases 15 and 16). Occasional low α_1-

TABLE 2.—SERUM PROTEINS IN HEMOCHROMATOSIS EXPRESSED IN GM. PER 100 ML.

Patient No.	*Albumin*	*Globulins* α_1	α_2	β	γ	*Total Protein*	*A/G*
		Idiopathic Hemochromatosis					
1	4.15	.23	.79	.89	.75	6.80	1.6
2	3.73	.24	.62	.77	1.00	6.36	1.4
3	3.17	.19	.60	1.01	.86	5.84	1.2
4	3.35	.17	.56	.77	.91	5.75	1.4
5	1.91	.34	.66	1.50	1.69	6.10	.5
6	3.00	.35	.97	1.20	1.45	6.97	.7
7	3.50	.34	.61	1.07	.85	6.38	1.2
8	3.05	.35	.79	1.06	1.49	6.73	.8
9	3.69	.23	1.37	.90	1.23	7.42	1.0
10	3.10	.33	.81	1.10	1.08	6.42	.9
11	3.23	.19	.74	.48	.77	5.41	1.5
12	4.07	.28	2.48	.71	.66	8.21	1.0
13	3.37	.31	.99	1.10	1.24	7.01	.9
14	2.77	.22	.45	.60	1.96	6.00	.9
15	3.38	.26	.63	.64	.82	5.73	1.4
16	3.12	.27	.67	.49	.87	5.42	1.4
17	3.73	.34	1.56	.36	.48	6.48	1.4
Mean	3.31	.27	.77*	.86	1.06	6.41	1.1
Standard deviation	.52	.06	.43–1.4†	.30	.39	.73	.3
		Transfusion Hemochromatosis (Hypoplastic Anemia)					
18	3.71	.36	.46	.70	.52	5.75	1.8
19	3.74	.40	.64	1.01	.94	6.73	1.3
		Normal Values					
Mean	4.01	.40	.62	.86	.85	6.75	1.5
Standard deviation	.46	.07	.11	.14	.14	.61	.3

*Median (computed from the mean logarithm).
†Range (computed from the mean logarithm plus or minus two logarithmic standard deviations).

Bailey[23]). This hypothesis is consistent with the importance of the function of the liver in serum protein synthesis (Ewerbeck[8,9], Hoch-Ligeti and Hoch[17], Miller *et al.*[28], Roberts and White[36]).

The greatest alteration found in the present study was a reduction in the globulin values have been encountered in liver disease (Young and Webber[44]), but most of the reported values range from higher than normal (Ricketts *et al.*[35], Sterling *et al.*[40], Thorn, Armstrong and Davenport[41]) to normal (Martin[24,25], Rafsky *et al.*[33]). Similar

changes to those observed here in regard to β- and γ-globulins have been reported in patients with liver disease (Benhamou and Pugliese[2], Emmrich[7], Franklin *et al.*[11,12], Gutman[14], Hanada[15], Hartmann and Steinebach[16], Martin[24,25,26], Martirani *et al.*[27], Owen and Robertson[29], Popper *et al.*[32], Rafsky *et al.*[33], Rath and Finch[34], Ricketts *et al.*[35], Schaffner, Scherbel and Lytle[38], Sterling *et al.*[40], Thorn, Armstrong and Davenport[41], Walker and Lev[42], Whitman, Rossmiller and Lewis[43], Young and Webber[44]) and with diabetes mellitus (Bowen[4], Klinger[18], Lewis *et al.*[20], Scheurlen[37]). In diabetes mellitus the α_2 globulin is elevated. The change of the β-globulin does not appear to involve the iron binding globulin which is a β_1-globulin and the level of which has been found to be normal in hemochromatosis (Rath and Finch[34]). It may be assumed, therefore, that the major serum protein changes in hemochromatosis are mainly due to the liver involvement or diabetes, or both, notwithstanding our failure to demonstrate their direct correlation to the estimated degree of these complications. It is of interest to note, however, that serum protein changes can be detected even in the early stages of hemochromatosis, when such complications may be absent or difficult to demonstrate. Thus, in addition to the low α_1-globulin found in cases 1 and 9, we have also observed high α_2- and γ-globulins (case 9), and low β-globulin with albumin at the lower limit of the normal range (case 16).

The α_2-globulin (cases 1, 3, 7, 12, and 13) and the γ-globulin (cases 3, 5, 6, and 13) exhibit a notable tendency to separate into 2 components. A similar tendency is exhibited by the α_2-globulin in hepatitis (Martirani *et al.*[27]) and by the γ-globulin in liver cirrhosis, where a fast γ_1-globulin is responsible for high fibrinogen values obtained electrophoretically (Franklin *et al.*[11,12]).

The negative correlation of the albumin with the β- and γ-globulins (*vide supra*) could be interpreted to mean that a compensatory mechanism may be responsible for the elevation of these components as the albumin falls. However, the absence of correlation between the α_1- and α_2-globulins with the other serum proteins does not support this interpretation, but it indicates that a basic defect in the protein metabolism must be responsible, at least in part, for the changes of the serum proteins in hemochromatosis. This has been shown to be true in liver cirrhosis (Martin and Davies[26], Thorn, Armstrong and Davenport[41]).

None of the observed alterations in hemochromatosis can be considered as specific or diagnostic on the basis of the available evidence. A possible exception to this is the α_1-globulin which, even in uncomplicated cases, was found to be distributed over a considerably lower range of values than those reported in liver cirrhosis. This observation suggests that a specific alteration of the metabolism of α_1-globulin in idiopathic hemochromatosis may exist, but additional studies in early uncomplicated cases and family members are needed to confirm this suggestion.

Summary. Electrophoretic studies of the serum proteins in 17 cases of idiopathic hemochromatosis were performed. Statistical analysis of the data showed that the mean values for the amount of albumin and particularly that of α_1-globulin are significantly lower and the mean for γ-globulin is significantly higher than normal. No significant difference from normal was observed in the mean values of the total protein and β-globulin. A greater than normal variance was encountered in the β-globulin. The α_2-globulin was

found to follow a log-normal distribution with a median slightly higher than the normal mean and an appreciable number of considerably higher than normal values. The A/G ratio was significantly lower than normal.

With the possible exception of α_1-globulin change it is probable that the serum protein alterations demonstrated in patients with idiopathic hemochromatosis are a reflection of impairment of liver function and diabetes mellitus.

REFERENCES

1. **Althausen, T. L., Doig, R. K., Weiden, S., Motteram, R., Turner, C. N.,** and **Moore, A.:** A.M.A. Arch. Int. Med., **88,** 553, 1951.
2. **Benhamou, E.,** and **Pugliese, J.:** Bull. Acad. Nat. Med., **134,** 772, 1950.
3. **Bodard, P., Osinski, P.,** and **Stein, F.:** Annales d'endocrinologie, **14,** 477, 1953.
4. **Bowen T. J.:** Brit. J. Exper. Path., **33,** 70, 1951.
5. **Cagli, V., Napolitano, L.,** and **Scuro, L.:** Policlinico (sez. prat.), **62,** 789, 1955.
6. **Deardorff, W. L.,** and **Kuhl, W. J., Jr.:** Bull. Northwest. Univ. Med. School, **30,** 107, 1956.
7. **Emmrich, R.:** Plasma, **1,** 495, 1953.
8. **Ewerbeck, H.:** Ztschr. ges. exper. med., **117,** 237, 1951.
9. Idem.: Ztschr. Kinderh., **70,** 481, 1952.
10. **Finch, S. C.,** and **Finch, C. A.:** Medicine, **34,** 381, 1955.
11. **Franklin, M., Bean, W. B., Paul, D., Routh, J. I., de la Huerga, J.,** and **Popper, H.:** J. Clin. Invest., **30,** 718, 1951.
12. Iidem.: Ibid., **30,** 729, 1951.
13. **Gray, S. J.,** and **Guzman Barron, E. S.:** Ibid., **22,** 191, 1943.
14. **Gutman, A. B.:** Advances in Protein Chemistry, **M. L. Anson** and **J. T. Edsall,** Eds., New York: Academic Press, Inc., vol. 4, p. 155, 1948.
15. **Hanada, S.:** Fukuoda Acta Med., **45,** 821, 1954.
16. **Hartmann, F.,** and **Steinebach, K.:** Deutsch. Arch. Klin. Med., **197,** 568, 1950.
17. **Hoch-Ligeti, C.,** and **Hoch, H.:** Brit. J. Exper. Path., **31,** 138, 1950.
18. **Klinger, R.:** Arch. Sci. Med., **95,** 141, 1953.
19. **Koenig, V. L., Weiger, R. W.,** and **Sowinski, R.:** J. Lab. & Clin. Med., **47,** 862, 1956.
20. **Lewis, L. A., Schneider, R. W., McCullagh, E. P.,** and **Clark, J.:** J. Clin. Endocrinol., **4,** 535, 1944.
21. **Longsworth, L. G.:** J. Am. Chem. Soc., **61,** 529, 1939.
22. Idem.: Chem. Rev., **30,** 323, 1942.
23. **Marble, A.,** and **Cabell Bailey, C.:** Am. J. Med., **11,** 590, 1951.
24. **Martin, N. H.:** Brit. J. Exper. Path., **27,** 363, 1946.
25. Idem.: Ibid., **30,** 231, 1949.
26. **Martin, N. H.,** and **Davies, H.:** Lancet, **2,** 1011, 1955.
27. **Martirani, L., Wajchenberg, B. L., Hoxter, G.,** and **Ulhoa Cintra, A. B.:** Gastroenterology, **30,** 286, 1956.
28. **Miller, L. L., Bly, C. G., Watson, M. L.,** and **Bale, W. F.:** J. Exper. Med., **94,** 431, 1951.
29. **Owen, J. A.,** and **Robertson, R. F.:** Lancet, **2,** 1125, 1956.
30. **Perlmann, G. E.,** and **Longsworth, L. G.:** J. Am. Chem. Soc., **70,** 2719, 1948.
31. **Poli, E., Caspani, R., Jucker, S.,** and **Villa, A. M.:** Minerva med., **1,** 1414, 1953.
32. **Popper, H., Bean, W. B., de la Huerga, J., Franklin, M., Tsumagari, Y., Routh, J. I.,** and **Steigman, F.:** Gastroenterology, **17,** 138, 1951.
33. **Rafsky, H. A., Weingarten, M., Krieger, C. H., Stern, K. G.,** and **Newman, B.:** Gastroenterology, **14,** 29, 1950.
34. **Rath, C. E.,** and **Finch, C. A.:** J. Clin. Invest., **28,** 79, 1949.
35. **Ricketts, W. E., Sterling, K., Kirsner, J. B.,** and **Palmer, W. L.:** Gastroenterology, **13,** 205, 1949.
36. **Roberts, S.,** and **White, A.:** J. Biol. Chem., **180,** 505, 1949.
37. **Scheurlen, P. G.:** Klin. Wchnschr., **33,** 198, 1955.
38. **Shaffner, F., Scherbel, A. L.,** and **Lytle, R. I.:** J. Lab. & Clin. Med., **48,** 551, 1956.
39. **Snedecor, G. W.:** Statistical Methods, Iowa City: The Iowa State College Press, 1946.

40. **Sterling, K., Ricketts, W. E., Kirsner, J. B.,** and **Palmer, W. L.:** J. Clin. Invest., **28,** 1236, 1949.
41. **Thorn, G. W., Armstrong, S. H., Jr.,** and **Davenport, V. D.:** Ibid., **25,** 304, 1946.
42. **Walker, H. M.,** and **Lev, J.:** Statistical Inference, New York: H. E[illegible] and Co., 1953.
43. **Whitman, J. F., Rossmiller, H. R.,** and **Lewis, L. A.:** J. Lab. & Clin. Med., **35,** 167, 1950.
44. **Young, E. G.,** and **Webber, R. V.:** Canad. J. Med. Sci., **31,** 45, 1953.

SUMMARIO IN INTERLINGUA

Studios Electrophoretic De Proteinas Seral In Hematochromatosis

Esseva effectuate studios electrophoretic del proteinas seral in 17 casos de hematochromatosis idiopathic. Le analyse statistic del datos monstra que le valor medie pro le concentration de albumina e particularmente illo pro le concentration de globulina alpha$_1$ es significativemente plus basse que in subjectos normal e que, del altere latere, le valor medie pro le concentration de globulina gamma es significativemente plus alte. Nulle deviation significative ab le norma esseva notate in le valores medie pro proteina total e globulina beta. Un variantia plus que normal esseva constatate pro globulina beta. Esseva trovate que le globulina alpha$_2$ habeva un distribution logarithmic normal con un valor median levemente plus alte que le normal valor medie e con un numero considerabile de valores que esseva marcatemente plus alte que le norma. Le proportion inter albumina e globulina esseva significativemente plus basse que in subjectos normal.

Con le exception possibile del alteration de globulina alpha$_1$, il es probabile que le alterationes del proteina seral que esseva demonstrate in patientes con hematochromatosis idiopathic esseva un reflexion de dysfunction hepatic e de diabete mellite.

SUMMARIO IN INTERLINGUA

(Interlingua on page 559)

Le Uso De Trypsina Per Via Oral In Duo Diabeticos Con Le Syndrome Nephrotic: Reporto Preliminar

Grande doses de trypsina (30 mg per die) pote esser administrate per via oral durante periodos de plure menses sin risco de toxicitate de grado significative. Duo diabeticos con le syndrome nephrotic obteneva marcate grados de melioration clinic e laboratorial per le administration oral de grande doses de trypsina que esseva continuate durante prolongate periodos de tempore. Il es possibile que le clarification del processo infectori es un factor contributori in le effectos notate. Le question proque patientes con deficientia primari de insulina es influentiate favorabilemente per le administration de un exogene enzyma pancreatic es le base de speculationes interessante. A iste tempore le autores non es preparate a formular conclusiones definitive e insiste que multe studios additional es requirite tanto con respecto al infection renal como etiam con respecto al integre phase de infection nephrotic in le phenomeno del disfallimento renal.

THE DIURETIC EFFECTS OF HYDROCHLOROTHIAZIDE IN CONGESTIVE HEART FAILURE, CIRRHOSIS, CHRONIC RENAL DISEASE AND HYPERTENSION: PRELIMINARY REPORT BASED ON A STUDY OF 28 CASES*

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Chlorothiazide (Diuril) is a potent diuretic drug that has been extensively employed in congestive heart failure, cirrhosis, renal disease and hypertension (Aleksandrow, Wysznacka and Gajewski[1], Keyes and Berlacher[4], Laragh, Heinemann and Demartini[5]). Experiments conducted on dogs showed that its 3,4-dihydro derivative, hydrochlorothiazide (Hydrodiuril) produced a marked increase in sodium and chloride excretion but relatively little increase in the excretion of potassium. It was found that hydrochlorothiazide was ten times as potent as chlorothiazide administered orally (Beem[3]). However, in human subjects, preliminary data indicate that hydrochlorothiazide is six to seven times as potent as chlorothiazide (Moyer *et al.*[7]). This present study was undertaken to evaluate the efficacy of this new oral diuretic in clinical states of abnormal fluid and salt retention.

Material and Methods. Twenty-eight patients ranging in age from 22 to 94 years of age were selected from the medical wards of the Philadelphia General Hospital (Table 1). These patients for the most part could not be controlled on an ambulatory basis. These patients may be considered to have a more advanced grade of heart disease and the therapeutic results would be less satisfactory than most patients encountered in the general office practice. The cases consisted of the following: congestive heart failure (15 cases), portal cirrhosis (6 cases), chronic renal disease (4 cases) and hypertension (3 cases). Edema was due to congestive heart failure secondary to arteriosclerotic heart disease (11 cases), rheumatic heart disease (2 cases), congenital heart disease (1 case) and idiopathic myocardial hypertrophy (1 case). With two exceptions, the patients were on digitalis therapy prior to the administration of hydrochlorothiazide. The severity of the congestive heart failure classified according to the New York Heart Association was as follows: Class IV (9 patients), Class III (5 patients) and Class II (1 patient). Four such patients were refractory to other diuretics. Five of the 6 patients with portal cirrhosis who had ascites and peripheral edema manifested little or no response to mercurial diuretics, given prior to or after hydrochlorothiazide therapy. Of 4 patients with chronic renal disease, 3 were in a terminal condition when treatment was begun.

Except for 2 patients on ulcer diets, patients were given the regular low salt hospital diet which contains approximately 1 gm. of sodium.

Venous blood pH, plasma sodium, potassium, magnesium, chloride, glutamic oxalacetic acid transaminase, creatinine and uric acid were obtained prior to the administration of hydrochlorothiazide and once to twice weekly thereafter. A 24-hour urine specimen was collected daily for the determination of sodium, potassium and chloride. Serum bili-

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TABLE 1.—CLINICAL CHARACTERISTICS OF PATIENTS

No.	*Patient*	*Age*	*Sex*	*Diagnosis*	*Class*	*Duration of Treatment* (Days)*	*Daily Dosage*	*Result*
				Congestive Heart Failure				
1	F. B.	53	M	Arteriosclerotic heart disease	II	12	50 mg.	Good
2	W. L.	58	M	Arteriosclerotic heart disease	IV	8	100 mg.	Fair; hydrochlorothiazide cut because of hypopotassemia and frequent premature ventricular contractions
3	J. J.	49	M	Arteriosclerotic heart disease	III	10	300 mg.	Good; hydrochlorothiazide reduced pt. to dry weight but plasma K rose from 5.8 to 7.4 mEq./L.
4	E. G.	40	M	Arteriosclerotic heart disease	IV	7	300 mg.	Poor; refractory to chlorothiazide and allergic to mercurials
5	W. M.	72	M	Arteriosclerotic heart disease	IV	10	300 mg.	Good
6	J. I.	70	M	Arteriosclerotic heart disease	IV	3	300 mg.	Good
7	J. W.	52	M	Arteriosclerotic heart disease; chronic pulm. disease	IV	11	300 mg.	Poor; refractory to chlorothiazide; fair response to mercurial diuretics
8	W. M.	49	M	Arteriosclerotic heart disease	IV	10	300 mg.	Good
9	O. G.	48	M	Arteriosclerotic heart disease	IV	5	300 mg.	Good
10	P. M.	62	F	Arteriosclerotic heart disease	IV	13	300 mg.	Good
11	J. M.	80	M	Arteriosclerotic heart disease Pelvic vein obstruction	III	6	300 mg.	Good

12	N. F.	57	M	Rheumatic heart disease	III	19	150 mg.	Poor; refractory to mercurial diuretics
13	A. P.	27	F	Rheumatic heart disease; cardiac cirrhosis	IV	5	300 mg.	Poor; fair response to mercurial diuretics
14	F. E.	38	M	Interatrial septal defect	III	17	300 mg.	Good; after diuresis for 17 days maintained in 50 mg. daily
15	J. B.	37	M	Idiopathic myocardial hypertrophy	III	7	300 mg.	Good
16	D. B.	22	M	Cirrhosis		16	100–300 mg.	Good initially but refractory after 10 days
17	D. T.	59	M	Cirrhosis		16	150–300 mg.	Fair initially but refractory on second trial; refractory to mercurial diuretics
18	S. F.	52	M	Cirrhosis		10	150 mg.	Good
19	E. S.	29	F	Cirrhosis		13	300 mg.	Good diuresis but patient went into impending hepatic coma with hypopotassemia which responded to treatment
20	E. M.	60	F	Cirrhosis		3	300 mg.	Poor
21	A. A.	46	M	Cirrhosis		2	50 mg.	Had hypopotassemia prior to treatment which was further aggravated
22	V. L.	45	F	Chronic renal disease		13	300 mg.	Fair
23	E. H.	80	F	Chronic renal disease		3	300 mg.	Poor
24	A. W.	79	F	Chronic renal disease		7	300 mg.	Poor
25	W. P.	71	M	Chronic renal disease		3	300 mg.	Poor
26	T. B.	52	M	Hypertension		8	150 mg.	Increase in Na excretion; lowering of blood pressure
27	T. T.	52	F	Hypertension		10	100 mg.	Increase in Na excretion; no effect on blood pressure
28	W. Y.	44	M	Hypertension		7	150 mg.	Increase in Na excretion; lowering of blood pressure

*Indicates length of time patients were followed with urinary electrolyte determinations; patients were given hydrochlorothiazide for longer periods for maintenance (up to 6 weeks).

rubin, total protein, albumin, globulin, cholesterol, alkaline phosphatase, cephalin flocculation, thymol turbidity and thymol flocculation were obtained prior to and after hydrochlorothiazide therapy in the group with congestive heart failure (5 cases), portal cirrhosis (4 cases), chronic renal disease (2 cases) and hypertension (2 cases).

Initially, the daily dosage of hydrochlorothiazide ranged from 50 to 150 mg. Later, this was increased to 100 mg. three times a day.

Based upon loss of body weight, reduction of peripheral edema and ascites, and salt excretion, the response to the drug was graded as "good," "fair" and "poor." A response was considered "good" if there was a reduction toward dry weight, "fair" if there was some diuresis but not complete control of the edema fluid, and "poor" if there was little or no diuresis.

Results. DIURETIC RESPONSE. Table 1 shows the pertinent clinical data of the patients treated and their response to hydrochlorothiazide. Figures 1 to 4 depict the characteristic response in representative cases of congestive heart failure and portal cirrhosis. Ten of 15

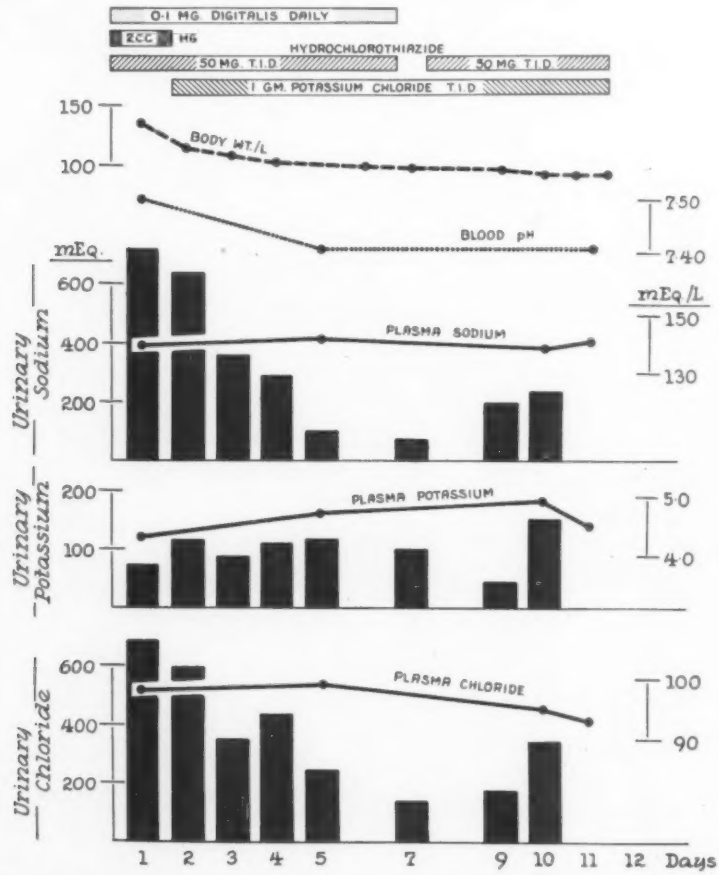

Fig. 1.—Shows the typical response to hydrochlorothiazide in a patient (Case 5, W.M.) a 72-year-old Negro male with congestive heart failure secondary to arteriosclerotic heart disease who was admitted with massive peripheral edema and bilateral pleura effusions. Administration of a mercurial diuretic resulted in a dramatic response which was maintained with hydrochlorothiazide. Withdrawal of hydrochlorothiazide on day 7 caused urinary electrolyte excretion to fall to their lowest level. Reinstitution of hydrochlorothiazide resulted in increased excretion.

patients with congestive heart failure manifested a good response. Weight loss ranged from 4 to 45 pounds over a period of 3 to 17 days with an average of 2.4 pounds a day. Three patients who were refractory to hydrochlorothiazide were also refractory to chlorothiazide. However, the administration of a mercurial diuretic produced a fair diuresis in two of these patients. In one patient, hydrochlorothiazide was more effective than a mercurial diuretic.

In 6 patients with ascites associated with cirrhosis, 5 initially showed a fair or good response to hydrochlorothiazide, but only 2 patients were reduced to "dry weight." Continued treatment with hydrochlorothiazide in the other patients failed to reduce the ascites. In one patient who became refractory to hydrochlorothiazide, clorothiazide likewise failed to produce a diuresis. In 3 cases (16, 17, 18) hydrochlorothiazide and mercurial diuretics were compared, and it was found that hydrochlorothiazide was as effective as the mercurials in 2 cases (17, 18) but not in a third (16).

In 4 patients with chronic renal disease associated with uremia and hypoalbuminemia, hydrochlorothiazide gave

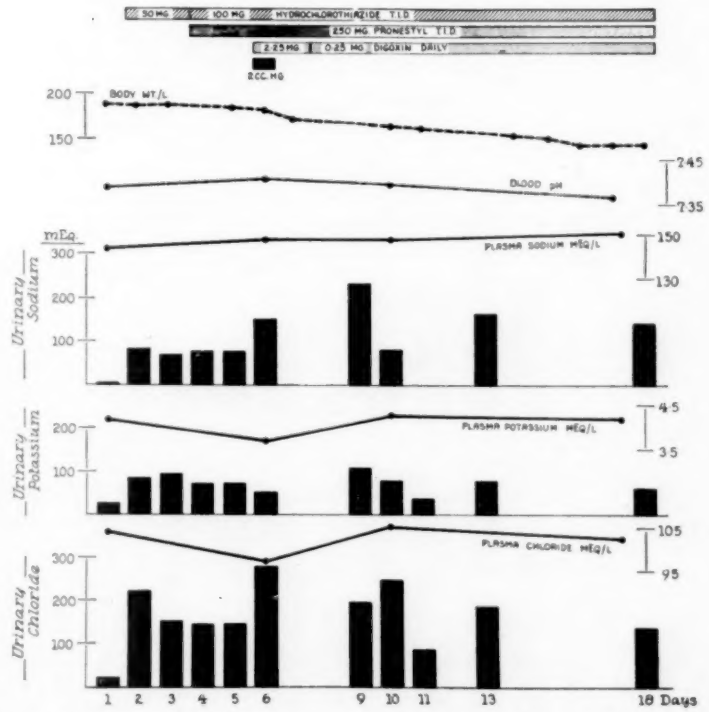

Fig. 2.—Shows the effect of hydrochlorothiazide and adjutant effects of digitalis and mercurial diuretics in a patient (Case 14, F.E.) a 38-year-old Negro male with congestive heart failure secondary to interatrial septal defect. Although the patient was kept at bedrest 3 days prior to the control, urine sodium excretion was negligible. A good response occurred with hydrochlorothiazide and was further potentiated by administration of digoxin and one dose of a mercurial diuretic.

a fair response in one and no diuretic response in the others.

ELECTROLYTE EXCRETION. The most striking alteration in the urine of the patients treated with hydrochlorothiazide was a marked increase in chloride (Table 2). This occurred in all but 3 cases. In those patients who had a good water diuresis, sodium excretion paralleled water loss. In 5 patients with portal cirrhosis and 3 patients with congestive heart failure, considerable amounts of potassium were excreted. Three nonedematous hypertensive patients showed increased excretion of sodium, potassium and chloride which was associated with a significant lowering of the diastolic pressure.

BLOOD pH AND PLASMA ELECTROLYTES. Individual blood pH and plasma potassium values are listed in Table 3. Seventeen patients had blood pH determinations prior to administration of hydrochlorothiazide and during treatment; of these, 10 remained normal, 3 became acidotic and 2 alkalotic. In one patient, the blood pH, which was acidotic prior to treatment, remained

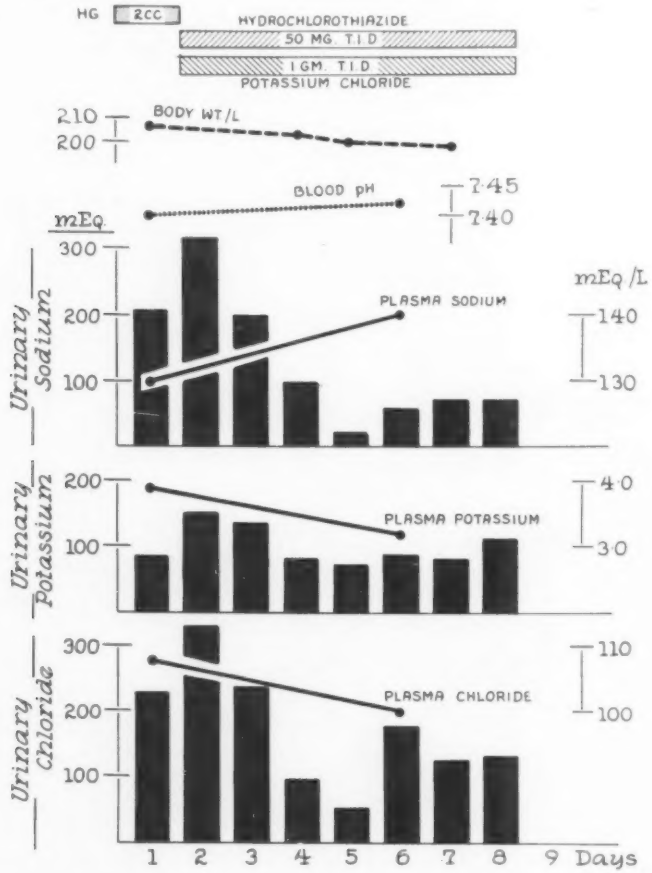

Fig. 3.—Shows the diuretic effect of hydrochlorothiazide in a cirrhotic (Case 18, S.F.) a 52-year-old white man. Considerable amounts of potassium excretion resulted in hypopotassemia.

acidotic, while in another the pH changed from alkalotic to normal. Eight patients had a reduction in plasma potassium ranging from 0.5 to 1.6 mEq. per L., with an average of 0.9 mEq. per L. Seventeen patients showed a reduction of plasma chloride ranging from 4 to 27 mEq. per L. with an average of 10 mEq. per L.; this did to hydrochlorothiazide therapy, the uric acid levels decreased in 4, increased in 2, and were unchanged in 2 patients.

TOXIC EFFECTS. In general, the patients tolerated the drug well. There were no gastrointestinal disturbances or skin reactions. Questionable somnolence was produced in one patient and

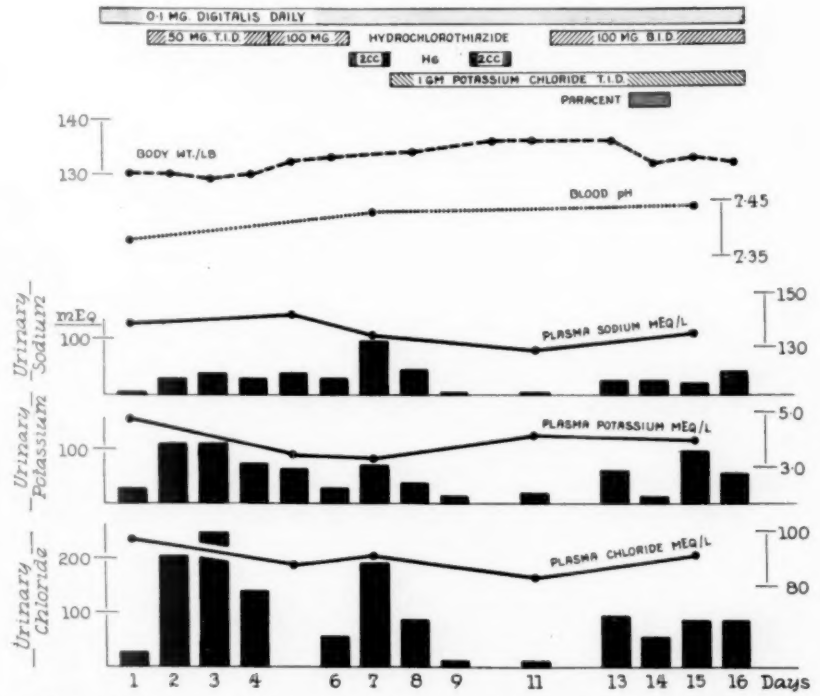

Fig. 4.—Shows the failure of adequate response to hydrochlorothiazide in a cirrhotic (Case 17, D.T.) 59-year-old white man. Although electrolyte excretion increased on initial administration of hydrochlorothiazide, water diuresis was minimal. A second trial beginning on the 12th day produced even less diuresis. Mercurial diuretics were likewise ineffectual.

appear to hinder the diuretic effect of hydrochlorothiazide. No significant changes were noted in plasma sodium and magnesium levels.

PLASMA URIC ACID. There were 3 patients with normal uric acid levels who evidenced hyperuricemia on therapy. All had renal disease. In 8 patients where hyperuricemia was present prior an increase in ventricular premature contractions was produced in another. There was no increase in glutamic oxalacetic transaminase. In 13 patients in whom complete liver profiles were carried out, there was no evidence of an alteration in hepatic function.

The most important untoward effect of hydrochlorothiazide was the devel-

opment of hypopotassemia, which occurred in 4 patients. A pre-existing hypopotassemia was aggravated in 2 additional patients. The reduction of plasma potassium was associated with impending hepatic coma in 2 cirrhotics. Withdrawal of the drug and administration of potassium relieved the symptoms. In case 19 (Table 1) reinstitution of hydrochlorothiazide in conjunction with potassium chloride and neomycin therapy resulted in a diuresis of 16 lb. in 11 days and there was no recurrence of hepatic coma.

TABLE 2.—URINARY EXCRETION OF ELECTROLYTES

		Control Levels 24 hr. (mEq.)			*After Hydrochlorothiazide Peak Levels 24 hr. (mEq.)**		
No.	*Patient*	*Na*	*K*	*Cl*	*Na*	*K*	*Cl*
1	F.B.	48	42	63	130	55	130
2	W. L.	35	56	80	79	154	145
3	J. J.	175	25	150	228	32	200
4	E. G.	53	97	78	49	74	85
5	W. M.	70	97	127	633	111	585
6	J. I.				132	30	171
7	J. W.	43	50	30	48	38	142
8	W. M.	128	13	132†	258	47	306
9	O. G.	65	11	71	208	34	219
10	P. M.	76	17	72	260	106	290
11	J. M.				96	18	148
12	N. F.	74	62	80	56	153	162
13	A. P.	45	15	70	23	22	39
14	F. E.	3	21	20	80	80	219
15	J. B.	34	49	50	302	54	364
16	D. B.	27	34	15	184	62	90
17	D. T.	1	25	25	37	105	247
18	S. F.	203	84	227†	315	148	325
19	E. S.	45	30	65	24	100	80
20	E. M.	1	2	4	11	15	29
21	A. A.	11	15	29			
22	V. L.	36	20	36	105	70	120
23	E. M.	18	11	26	39	23	42
24	A. W.	18	13	38	33	28	38
25	W. P.	38	23	42	40	15	40
26	T. B.	64	49	71	100	40	151
27	T. T.	11	19	48	91	53	131
28	W. Y.	41	29	57	190	65	229

*Based on day that chloride peaked
†Mercurial diuresis

Discussion. MODE OF ACTION. The exact mechanism by which hydrochlorothiazide acts as a diuretic has not been definitely established. Its parent compound, chlorothiazide appears to inhibit renal tubular absorption of sodium and chloride resulting in a secondary increase in water excretion. Also, some carbonic anhydrase inhibition on the renal tubules is noted, particularly at larger doses (Moyer *et al.*[7]).

DIURETIC EFFECTIVENESS. Hydrochlorothiazide is a potent oral diuretic agent. It was most effective in patients with congestive heart failure. It failed to cause diuresis in patients who were refractory to chlorothiazide or to the mercurial diuretics. Although direct comparisons between hydrochlorothiazide and chlorothiazide were not made except in 5 patients, it was our impression from this and our previous studies (Aytur and Bellet[2]), that the drugs are comparable in their action and side

effects. Hydrochlorothiazide offered no significant advantages over chlorothiazide.

ELECTROLYTE EXCRETION. Hydrochlorothiazide resulted in the excretion of considerable amounts of chloride with sodium and potassium in varying proportions. Unlike the results of animal experiments which indicated minimal potassium excretion, upon hydrochlorothiazide administration considerable amounts of potassium were excreted in human subjects, particularly in patients with portal cirrhosis and some with congestive heart failure. It is felt that patients with liver disease and those receiving hydrochlorothiazide over prolonged periods should be supplemented with oral potassium. One gram of potassium chloride three to four times a day is recommended in such patients.

ANALYSIS OF FAILURES. Eight patients showed a poor response to hydrochlorothiazide. Six of these patients had either renal or hepatic disease associated with hypoalbuminemia. One of the patients was on an ulcer diet which contained large amounts of salt. It is not to be inferred that hypoalbuminemia is the primary cause of failures because diuresis occurred in 3 patients with hypoalbuminemia. Many factors were responsible in addition to the hypoalbuminemia, notably advanced congestive heart failure, renal disease, liver disease and refractory types of electrolyte imbalance.

TOXICITY. Hydrochlorothiazide appears to be a safe, well-tolerated drug.

TABLE 3.—BLOOD pH AND PLASMA POTASSIUM LEVELS BEFORE AND AFTER HYDROCHLOROTHIAZIDE

		Control							
No.	*Patient*	*pH*	*K (mEq./L.)*	*Day of Therapy*	*pH*	*K (mEq./L.)*	*Day of Therapy*	*pH*	*K (mEq./L.)*
1	F. B.	7.39	4.1	4	7.37	4.3	12	7.32	4.3
2	W. L.	7.42	3.1	3		3.0			
3	J. J.	7.35	5.8	4	7.22	6.6	7		7.7
4	E. G.	7.44	4.4	5	7.53	4.5			
5	W. M.	7.49	4.3	4	7.41	4.7	10	7.41	4.5
6	J. I.	7.37	3.2						
7	J. W.	7.30	4.3	5		4.4	10	7.28	4.6
8	W. M.	7.35	4.4	3	7.40	3.8	12	7.32	4.7
9	O. G.	7.36	4.6	5		5.3			
10	P. M.	7.43	3.0	7	7.45	3.3			
11	J. M.	7.34	4.7	6	7.39	4.7	6	7.39	4.7
12	N. F.	7.42	5.6	4	7.31	5.6	19	7.38	4.6
13	A. P.		2.7	2		4.9	5		5.5
14	F. E.	7.38	4.2	5	7.41	3.7	16	7.37	4.2
15	J. B.	7.39	4.4	5	7.42	4.7	16		
16	P. B.	7.36	4.3	6		4.7	15	7.39	4.4
17	D. T.	7.38	4.7	6	7.43	3.3	10	7.44	4.0
18	S. F.	7.40	3.9	5	7.41	3.2			
19	E. S.	7.38	4.9	3	7.48	3.3			
20	E. M.		3.9	3		4.0			
21	A. A.	7.44	2.8	2		2.1			
22	V. L.	7.34	4.2	6	7.39	3.5	13	7.40	3.6
23	E. H.	7.46	5.1	3		5.0			
24	A. W.	7.34	3.7	4	7.42	4.8			
25	W. P.		3.9						
26	T. B.	7.35	5.4						
27	T. T.	7.40	4.0	8	7.32	3.9			
28	W. Y.	7.40	4.4	7	7.40	3.3			

It has the same shortcomings as its parent compound, chlorothiazide, that is, a tendency to produce hypopotassemia. Compared with a comparable group of patients on Diuril studied in this hospital, no significant difference in the degree of hypopotassemia was noted (Aytur and Bellet[2]). It may also induce impending hepatic coma as has been noted with chlorothiazide (Mackie *et al.*[6]). By close observation and supplementary oral potassium, these untoward effects may be avoided.

Summary. Hydrochlorothiazide, a derivative of chlorothiazide was tested for its diuretic effectiveness in patients with congestive heart failure, cirrhosis, chronic renal disease and hypertension. It was found to be a potent oral diuretic particularly in patients with congestive heart failure. It was of limited value in patients with cirrhosis and renal disease. Chloride was excreted in considerable amounts with sodium and potassium in varying proportions. The most important untoward effect was the development of hypopotassemia secondary to increased potassium excretion. This was particularly marked in patients with liver disease. It was our impression that hydrochlorothiazide was comparable to chlorothiazide in diuretic effectiveness.

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REFERENCES

1. **Aleksandrow, D., Wysznacka, W.,** and **Gajewski, J.:** New England J. Med., **260,** 51, 1959.
2. **Aytur, M.,** and **Bellet, S.:** Unpublished observations.
3. **Beem, J.:** Personal communication.
4. **Keyes, J. W.,** and **Berlacher, F. J.:** J. Am. Med. Assn., **169,** 109, 1959.
5. **Laragh, J. H., Heinemann, H. O.,** and **Demartini, F E.:** Ibid., **166,** 145, 1958.
6. **Mackie, J. E., Stormont, J. M., Hollister, R. M.,** and **Davidson, C. S.:** New England J. Med., **259,** 1151, 1958.
7. **Moyer, J. H., Fuchs, M., Irie, S.,** and **Bodi, T.:** Am. J. Cardiol., **3,** 113, 1959.

SUMMARIO IN INTERLINGUA

Le Effectos Diuretic De Hydrochlorothiazido In Congestive Disfallimento Cardiac, Cirrhosis, Chronic Morbo Renal, E Hypertension: Reporto Preliminar, Basate Super Un Studio De 28 Casos

Hydrochlorothiazido, un derivato de chlorothiazido, esseva testate pro su efficacia diuretic in patientes con congestive disfallimento cardiac, cirrhosis, chronic morbo renal, e hypertension. Esseva constatate que illo es un potente diuretico oral, specialmente in patientes con congestive disfallimento cardiac. Illo esseva de valor plus tosto restringite in patientes con cirrhosis e morbo renal. Chloruro esseva excernite in quantitates considerabile, natrium e kalium in varie proportiones. Le plus importante effecto adverse esseva le disveloppamento de hypokaliemia como resultato secundari del augmentate excretion de kalium. Isto esseva specialmente marcate in patientes con morbo hepatic. Nostre impression esseva que hydrochlorothiazido es comparabile chlorothiazido in su efficacia diuretic.

A SIMPLIFIED METHOD FOR THE RECTAL INSTILLATION OF THEOPHYLLINE

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The therapeutic effectiveness of theophylline is well known, and maximum response is obtained by intravenous administration. This route has serious disadvantages, however, which include, in addition to the inherent discomfort of venipuncture, the danger of serious cardiac arrhythmia and death if the drug is injected too rapidly (Bresnick, Woodard and Sageman[2]).

Oral administration may give rise to gastric irritation, nausea, and vomiting (Goodman and Gilman[4]). Furthermore, a portion of theophylline is metabolized in passage through the liver.

Since rectal absorption permits entrance into the inferior vena cava, a greater proportion of the administered dose of theophylline may reach the pulmonary and peripheral circulation after administration by this route than would occur with a comparable amount given orally. The customary rectal dosage form has been a suppository, but absorption from a suppository may be slow and erratic. This disadvantage is the result of an unfavorable distribution coefficient of the medication between suppository base and aqueous phase of rectal mucous membrane. In order to promote better absorption, a water soluble form of the drug has been given as a retention enema. Such a preparation eliminates all barriers to diffusion of the drug into the mucosa and makes a more prompt absorption possible.

Barach[1] reported on the effects of an aqueous solution of theophylline as an enema in more than 200 patients with bronchial asthma. His patients found that relief of bronchospasm occurred in 10 to 20 minutes. No side-effects were reported. He reported that the availability of self-medication by enema far outweighed any possible loss of uniformity in absorption when the drug is given by enema rather than intravenously. Indeed, Truitt, McKusick, and Krantz[7] found theophylline to be very effective when given by retention enema.

The rectal route has not yet met with widespread acceptance. The inconvenience of preparing an enema has limited the acceptance of this method of administration. This disadvantage has been eliminated by the development of a convenient plastic unit with proper rectal applicator attached. Each unit contains 37 ml. of 16.6% W/V solution of theophylline monoethanolamine.* This convenient preparation

*Clysmathane: C. B. Fleet Company, Inc., Lynchburg, Virginia.

makes possible the administration of theophylline in a readily absorbable, nonirritant form.

The disposable enema unit, kindly provided by Sidney G. Page, Jr., M.D., of C. B. Fleet Company, Inc. as Clysmathane, consists of a tough, flexible plastic container, a prelubricated rectal nozzle approximately 1½ inches long, a slit rubber diaphragm which controls the flow of liquid, and a sanitary cover cap which seals the unit and protects the nozzle when not in use. By compressing the container when the cap is removed, the theophylline solution can be readily expressed. Since 5 to 7 ml. of solution remains in the container after use, the patient receives a therapeutic dose of approximately 0.5 gm. of the drug.

Methods. Sixty-two patients with dyspnea associated with cardiac or pulmonary disease, or both, were selected for this study. Thirty-four males and 28 females participated in this study. Ages varied from 31 to 80. Twenty patients were hospitalized and the concentration of theophylline in the plasma was determined at definite intervals after administration of theophylline monoethanolamine* by various routes, that is, oral tablets, intravenous injection, and various techniques of rectal administration. The effectiveness of multiple dosages of theophylline was observed. Plasma concentrations of theophylline were determined by the method of Waxler and Schack[8] as modified by Carmichael[3].

During these studies, all other xanthine-containing medications were discontinued. In addition, the use of coffee, tea, and similar beverages was eliminated.

In one group, 10 patients' blood samples were obtained at 0, 15, 30, 180, and 300 minutes after administration of single doses of theophylline monoethanolamine in various forms; a second series involving 10 patients had plasma determinations at 0, 5, 10, 30, 60, 120, and 240 minutes. The patients were all selected at random and served as their own controls.

Theophylline monoethanolamine was instilled rectally by means of (1) a 6-inch catheter, (2) a disposable unit with a 1½ inch nozzle, by patient and by nurse, and (3) a suppository. In an attempt to simulate the conditions of clinical usage, no effort was made to cleanse the rectum of feces before the rectal administrations. The same dose was also given orally as a timed disintegrating tablet† and intravenously.

In order to determine the therapeutic effectiveness of the rectal instillation of theophylline, 8 patients, 4 with pulmonary emphysema and 4 with cardiac asthma, were given Clysmathane for one to 7 days on a multiple dose schedule. Six of these patients were able to administer the rectal solution without assistance; because of debility, 2 patients were assisted by the nurse. The medication was given two, three, or four times daily. Theophylline plasma concentrations were determined 2 to 5 hours after the last dose.

Forty-two patients used the disposable units on an outpatient basis over a period of 3 months. Five of the patients were asthmatic. The remainder had cardiovascular disease with a functional severity of Class II to Class III (classification of the New York Heart Association[6]). Eleven patients had hypertensive cardiovascular disease, 3 had aortic insufficiency, and the remainder had arteriosclerotic heart disease.

All patients had respiratory difficulty. They were instructed to use the rectal units as needed to relieve cardiorespiratory distress. Three hundred doses were self-administered by these patients.

Results. The plasma theophylline levels obtained when the nurses instilled the rectal solutions were almost identical with the results obtained after self-administration. Therefore, these data were combined for evaluation. The response with the 6-inch catheter was similar to that obtained with the disposable unit. Plasma theophylline concentrations were reached much more slowly with suppositories than with the rectal instillation of the aqueous solution of theophylline monoethanolamine.

As expected, the use of timed disintegrating tablets was associated with

*Theamin, Eli Lilly and Co., Indianapolis, Indiana.

†Theamin, Enseal, Eli Lilly and Co., Indianapolis, Indiana.

a delay in absorption. The aqueous solution of theophylline was absorbed more promptly from the rectum than the suppositories (Fig. 1). Theophylline given intravenously produced the most rapid and highest plasma theophylline concentrations. However, a clinically effective plasma level of theophylline was obtained in one-half hour following rectal instillation of the complaint was paroxysmal nocturnal dyspnea. The use of theophylline monoethanolamine rectal solution before retiring diminished the number of such attacks and allowed an uninterrupted sleep. This was a subjective improvement and although no objective studies were performed which could be analyzed by statistical methods, the patients uniformly remarked on the

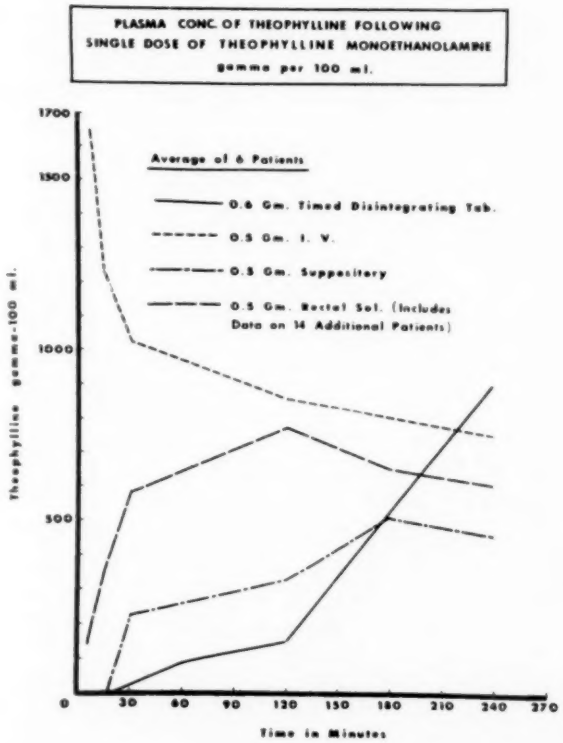

Fig. 1.

solution. Neither oral nor suppository administration of theophylline resulted in a comparable plasma level.

Repeated administration of the rectal unit produced plasma theophylline levels comparable to those achieved by intravenous administration (Table 1).

Of the 42 patients using this rectal unit as outpatients, 11 had hypertensive cardiovascular disease. Their main relief from and prevention of cardiac asthma with the use of this medicine.

Dyspnea and wheezing were markedly improved in all of the patients. Only 2 of these 42 patients expressed a preference for suppository over the aqueous rectal solution. The remainder recognized a more prompt and sustained response. Rectal irritation was not a problem.

TABLE 1.—THE RESPONSE TO THEOPHYLLINE MONOETHANOLAMINE RECTAL SOLUTION ON REPEATED ADMINISTRATION

Patient	*Diagnosis*	*Days of Treatment*	*Dose*	*Hr. After Last Dose*	*μg. 100 ml.*	*Remarks*	*G. I. Complaint*
J. H.	H.C.V.D. with Left Ventricular Failure	4	1 t.i.d. 1 t.i.d.	2 2	1520 1960	Improved breathing. No P.N.D.	None
C. B.	A.S.H.D. Cor Pulmonale	4	1 t.i.d. 1 t.i.d.	2 2	1220 1880	Improved breathing.	None
O. B.	Pulmonary Emphysema Bronchial Asthma	4	1 q.i.d. 1 q.i.d.	2 2	950 850	Improved breathing. Preferred suppository but requested solution on release.	None
J. D.	Bronchial Asthma Cor Pulmonale Congestive Heart Failure	1	1 t.i.d.	5	580	Improved breathing. "Felt better"	None
M. M.	Rheumatic Heart Disease	2	1 t.i.d.	5	1530	Weakness	Nausea but over-digitalized
W. G.	Pulmonary Emphysema Bronchial Asthma	7	1 b.i.d.		*	Preferred suppository. 1. Easier to handle 2. Easier to retain 3. No laxative effect 4. No staining of clothing	None
W. J.	Pulmonary Emphysema	7	1 b.i.d.		*	Improved breathing. Able to sleep per night without usual P.N.D.	None
D. H.	H.C.V.D. Cardiac Asthma	7	1 h.s.		*	Improved breathing. Able to sleep per night without usual P.N.D.	None

*Specimen not drawn.

Two patients were relieved of an acute asthmatic attack within one-half hour after administration of the rectal solution.

Discussion. The effectiveness of theophylline for relief of bronchial asthma and dyspnea, especially the paroxysmal form associated with hypertensive heart disease, is well known. According to Goodman and Gilman[5], it is a good smooth muscle relaxant and myocardial stimulant. The route of administration has constituted a problem which has limited the use of soluble forms of theophylline. Although the oral route would be the most convenient for treatment of chronic or recurrent disease, undesirable side-effects may occur due to gastric irritation. Although enteric coated tablets may be helpful in decreasing this side-effect, absorption from enteric coated tablets may be highly erratic. Further, a loss due to hepatic metabolism may reduce the effectiveness of theophylline when given orally. The intravenous injection has obvious limitations and may be dangerous.

The use of rectal suppositories has not produced dependable results nor has the relief of dyspnea been prompt. From observations of concentration of theophylline in the blood, it appears that the rectal instillation of theophylline monoethanolamine from the disposable unit will overcome all of the difficulties just described. The disposable unit provides an easy, convenient method for rectal use and makes self administration possible. In this form the drug can be given at the very onset of a paroxysm of dyspnea.

When properly instructed our patients preferred the rectal disposable units to insertion of suppositories. They recognized the prompt relief. The theophylline levels reported in these studies indicate adequate "physiologic" availability of theophylline when approximately 0.5 gm. is given as a monoethanolamine derivative in aqueous solution by rectal route. This is in keeping with the advantageous distribution coefficient provided in an aqueous vehicle.

Conclusions. A disposable rectal unit which provides a safe, effective, and convenient method for administering theophylline monoethanolamine as a therapeutic enema has been described.

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REFERENCES

1. **Barach, A. L.:** J. Am. Med. Assn., **128**, 589, 1945.
2. **Bresnick, E., Woodard, W. K.,** and **Sageman, C. B.:** Ibid., **136**, 397, 1948.
3. **Carmicheal, R.:** Personal communication.
4. **Goodman, L. S.,** and **Gilman, A.:** The Pharmacological Basis of Therapeutics. 2nd ed. New York: The MacMillan Company, p. 349, 1955.
5. Iidem: p. 340.
6. New York Heart Association, Inc., Criteria Committee: Nomenclature and Criteria for Diagnosis of Diseases of the Heart and Blood Vessels. H. E. B. Pardee, Chairman. 5th ed. p. 81, 1953.
7. **Truitt, E. B., Jr., McKusick, V. A.,** and **Krantz, J. C., Jr.:** J. Pharmacol. & Exper. Therap., **100**, 309, 1950.
8. **Waxler, S. H.,** and **Schack, J. A.:** J. Am. Med. Assn., **143**, 736, 1950.

SUMMARIO IN INTERLINGUA

Un Simplificate Methodo Pro Le Instillation Rectal De Theophyllina

Es describite un non-iterabile dispositivo rectal que provide un salve, efficace, e convenibile methodo pro le administration de monoethanolamina theophyllinic como clyster therapeutic.

VALUE OF SIMPLE LABORATORY PROCEDURES IN THE DIAGNOSIS OF CUSHING'S SYNDROME*

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From the time of the earliest recognition of Cushing's syndrome through the more recent studies of ACTH stimulation of the adrenal glands, mention has been made of the abnormality of simple and readily available laboratory tests. With the evolution of diagnostic primacy from physical appearance of the patient to application of steroid hormone determinations in blood and urine, meager attention has been given the use of these more mundane procedures. Despite rapid progress in hormonal assay, and granting the fact that consideration of Cushing's syndrome ordinarily stems from clinical recognition of its possibility, these simpler tests still appear to have utility, particularly to strengthen or weaken the diagnosis.

This report analyzes the value of differential leukocyte count, total eosinophil count, hematocrit, bone roentgenograms, glucose tolerance tests and measurement of blood pressure as adjuncts in the diagnosis of Cushing's syndrome.

Materials and Methods. Twenty patients were studied (all seen by one of us), 18 of whom had the diagnosis of Cushing's syndrome confirmed by levels of corticoid excretion and by operation. In the other 2 patients, classic clinical features and hormonal studies rendered the correct diagnosis unmistakable. Among the 18 cases with surgically proven diagnoses, there were 12 with hyperplasia, one with hyperplasia and adenoma formation, 4 with benign adenoma, and one with carcinoma. There were 16 female and 4 male patients.

The tests evaluated were as follows: The polymorphonuclear cells on the routine peripheral blood smear were counted and the average of three or more determinations evaluated. Total eosinophil counts were made by the technique of Randolph[20], at least 3 tests being averaged in each instance. Eosinophil counts on a large series of normal subjects at this institution average 149 per c.mm. ± 71 and values below 80 were more than one standard deviation from the mean (Maher and Kyle[16]). The glucose tolerance test was conducted in the standard manner, using 100 gm. of glucose as a test meal and was considered definitely abnormal if the 2-hour level was 50 mg. above the fasting, or the 3-hour specimen was 30 mg. above the control blood sugar value. The hematocrit was considered elevated if it exceeded 48% in the female or 53% in the male subjects. Rest-

*Supported in part by the William Wade Hinshaw Cancer Research Fund.

ing blood pressure was considered significantly elevated if it exceeded 160 systolic or 110 diastolic. The presence and degree of osteoporosis was judged by roentgenograms of the lateral lumbar spine, and considered present only if moderate or marked. Cases with generalized decreased density but without compression or Schmorl's bodies were not included. All laboratory procedures were done before adrenal stimulation or suppression tests were conducted.

cases had one or more of these hematologic abnormalities, Fig. 1.

With less rigid standards, that is, neutrophils 70% or above, eosinophils 80 per c.mm. or below and hematocrit 3% above normal, the number of positive tests increased. Polymorphonuclear leukocytosis was seen in 80%, eosinopenia in 85%, and 60% of the patients

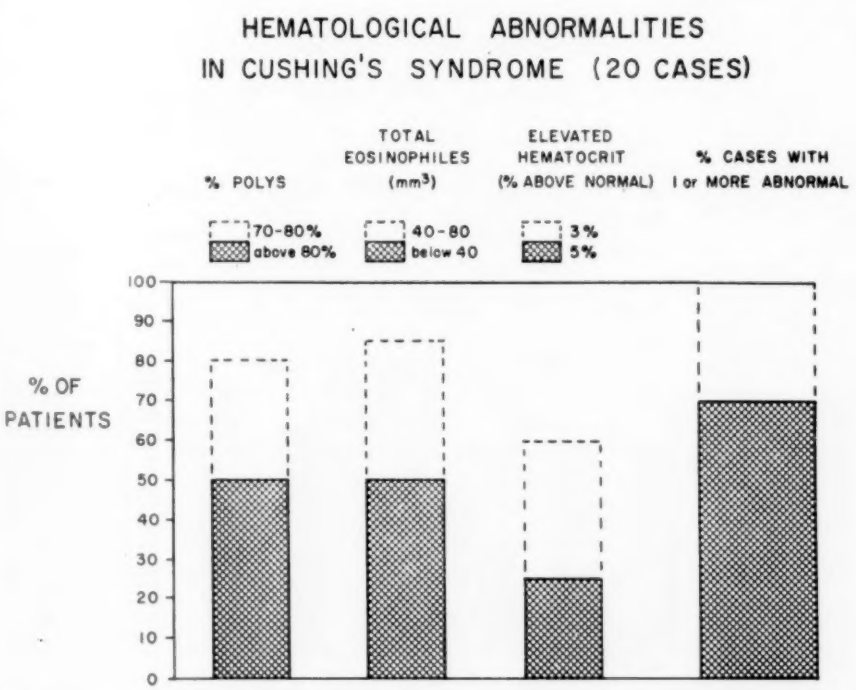

Fig. 1.—The percentage of patients with hematologic abnormalities in Cushing's syndrome is shown using strict (cross-hatched) and less rigid criteria (dotted extensions).

Results. Simple hematologic tests were considered significantly abnormal if the neutrophils exceeded 80%, the total eosinophil count was below 40 per c.mm., and the hematocrit exceeded the normal by at least 5%. As judged by these standards, 50% of the patients with Cushing's syndrome had significant elevation of neutrophils, 50% had eosinopenia, and 25% showed polycythemia. Seventy per cent of the 20 (all of them women) had elevation of the hematocrit. All patients showed at least one of these abnormalities. Ninety-five per cent demonstrated 2 or more, Fig. 1.

Figure 2 depicts the hematologic abnormalities, using the more strict criteria, as well as the incidence of osteoporosis, hypertension, and carbohydrate intolerance. Osteporosis was present in 60%, a similar number had

significant hypertension, and 70% demonstrated either overt diabetes or a clear-cut diabetic glucose tolerance test. Abnormality of one or more of these 3 manifestations was seen in all patients.

Table 1 summarizes the number of unequivocal abnormalities in each patient, which ranged from one to 5, the average being 3.2 in the entire series.

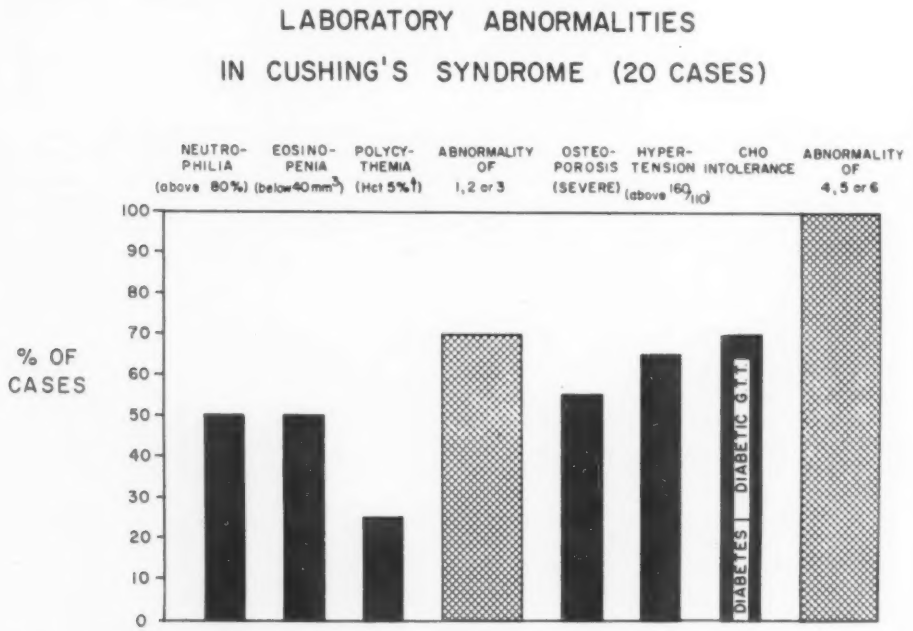

Fig. 2.—The incidence of single laboratory abnormalities and combinations thereof is shown. Strict criteria were used.

In only one case was a single abnormality found (Case 5, who had only a diabetic glucose tolerance test). This patient, however, showed florid clinical features of Cushing's syndrome and the diagnosis was readily made on physical inspection.

Discussion. Beginning with the writings of Cushing[4,5,6], the literature on adrenal cortical hyperfunction attests to the frequency of these laboratory abnormalities (Crooke[3], Eisenhardt and Thompson[9], Haymaker and Anderson[11], Oppenheimer and Silver[18], Walters, Wilder and Kepler[24]). Most impressions, however, have been drawn from reports with minimal data and little standardization. Furthermore, the few large series suffer from the inherent drawbacks of reports extracted from the records of cases seen by others, and from the variable standards of normal used for evaluation of these procedures.

HEMATOLOGIC ABNORMALITIES. Immediate and sustained eosinopenia after injection of ACTH in the presence of intact adrenal glands was first observed in 1948 (Hills, Forsham and Finch[12]). Eosinopenia has since been noted with the therapeutic use of ACTH and corticosteroids (Sprague *et al.*[23]) and has been emphasized as a feature of Cushing's syndrome by Plotz, Knowl-

ton and Ragan[19], who derived their data from differential white blood counts. With more rigid criteria and by direct counting, we have confirmed the high incidence of eosinopenia in adrenal hypercorticism. Unless some cause of stress is apparent, we consider the virtual absence of circulating eosinophils a significant finding deserving further investigation.

Polymorphonuclear leukocytosis, a frequent feature of Cushing's syndrome, is attributed to the observed neutrophilic and lymphopenic effect of ACTH and adrenal cortical extracts (Dougherty and White[8,26], Hills, Forsham and Finch[12]). Our results are in accord with those of DeLaBalze, Reifenstein and Albright[7] who found 80% or more neutrophils in 6, and 70% or more in 9 of their 10 cases. Neutrophilia in hyperadrenocorticism is more impressive in the presence of a normal total leukocyte count, and, like eosinopenia, marked neutrophilia is unusual in patients admitted under basal conditions for diagnostic study.

TABLE 1.—INDIVIDUAL LABORATORY ABNORMALITIES IN 20 PATIENTS WITH CUSHING'S SYNDROME

CASE	AGE	SEX	♀	POLYS OVER 80%	TOTAL EOSINOPHILES BELOW 40/mm³	HEMATOCRIT SIGNIFICANTLY ↑ above 48 in ♀ above 53 in ♂	DIABETES or DIABETIC G.T.T. 50 above fasting -2hr 30 above fasting -3hr	MODERATE or MARKED OSTEOPOROSIS	HYPERTENSION SYSTOLIC 160↑ DIASTOLIC 110↑	# ABNORMAL
1	38	F	?	■	■			■	■	5
2	39	F	HYPERPLASIA		■		D	■	■	4
3	33	M	?					■		2
4	24	F	HYPERPLASIA					■		2
5	23	F	HYPERPLASIA							1
6	12	F	HYPERPLASIA			■		■		2
7	42	F	HYPERPLASIA					■	■	3
8	43	F	HYPERPLASIA	■	■		D		■	4
9	34	F	HYPERPLASIA		■			■	■	3
10	48	F	HYPERPLASIA				D		■	2
11	22	M	HYPERPLASIA	■	■		D		■	4
12	41	M	HYPERPLASIA	■	■				■	4
13	29	F	HYPERPLASIA	■		■		■		4
14	23	F	HYPERPLASIA	■		■		■	■	5
15	29	F	HYPERPLASIA and ADENOMA					■	■	2
16	20	F	ADENOMA	■	■				■	3
17	43	F	ADENOMA	■		■		■	■	4
18	24	M	ADENOMA		■			■		2
19	34	F	ADENOMA (?CA)	■	■					3
20	40	F	CARCINOMA	■	■	■	D		■	5
				50%	50%	25%	70%	55%	65%	AVG. = 3.2

The mild polycythemia frequently seen in Cushing's syndrome has been documented to result from a single or repeated injections of ACTH or adrenal cortical extract (White and Dougherty[8,26]). The red blood count was 5 million per c.mm. or above in 50% of Cushing's cases[4,5] and in 48% of the series by Plotz, Knowlton and Ragan[19]. Both marked polycythemia (Sossman[22]) and anemia are infrequently

seen in hyperadrenocorticism. The only patient with anemia in this series developed it late in the course of a complicating bronchogenic carcinoma (Kovach and Kyle[15]).

OSTEOPOROSIS. It is hypothesized that in adrenal cortical hyperfunction excess gluconeogenesis results in decreased availability of amino acids and the consequent protein lack causes osteoporosis (Albright, Parson and Bloomberg[1]). In the series of Plotz, Knowlton and Ragan[19], 83% had spinal osteoporosis and 60% showed decalcification of the skull. Among the 38 cases of Cushing's disease studied by Wang and Robbins[25], the incidence of osteoporosis was 47%, 82%, 70% and 43% in the spine, skull, ribs, and pelvis. Backache is a common symptom and pathologic fractures may occur. While osteoporosis may be due to a wide variety of causes, it is not often seen in young adult women, the group in whom Cushing's syndrome most frequently occurs. The review of Cushing's syndrome in children by Farber, Gustina and Postoloff[10], revealed an impressive (75%) incidence of osteoporosis among 27 patients.

HYPERTENSION. Hypertension, long a known feature of hyperfunctioning adrenal cortical tumors (Kepler and Keating[13], Oppenheimer and Fishberg[17], Rowntree and Ball[21]), was noted in 92% of the cases in Knowlton's series[14] and blood pressure exceeded 150/95 in 83% of the 46 patients reported by Cope and Raker[2]. The somewhat lower incidence in our series probably reflects stricter criteria. Cushing's syndrome in childhood was attended by hypertension in 25 of 27 cases (Farber, Gustina and Postoloff[10]).

DIABETES. While overt diabetes may not be present in adrenal cortical hyperactivity, carbohydrate intolerance has been reported to occur in about 90% of cases (Cope and Raker[2], Plotz, Knowlton and Ragan[19]), often associated with resistance to insulin. Fourteen of our 20 cases manifested disturbed carbohydrate metabolism, 5 of whom had overt diabetes and 3 were resistant to insulin.

OTHER DATA. Neither hypernatremia nor hypokalemia were seen with sufficient frequency to be of diagnostic utility in this series of patients. Routine skull films and pyelograms were not of diagnostic aid.

Summary. The value of simple laboratory studies as an adjunct to the diagnosis of Cushing's syndrome was evaluated in 20 patients. Polymorphonuclear leukocytosis and eosinopenia of significant degree were observed in half the cases and striking increase in hematocrit was seen in 25% of the patients. One or more of these hematological abnormalities was present in 70% of the cases.

Moderate or marked osteoporosis occurred in 12 of the 20 patients and a similar number had hypertension. Overt diabetes or carbohydrate intolerance was present in a slightly greater number. Of the total of possible abnormalities, 2 or more were present in 19 patients and 3 abnormalities were apparent in the average case.

Careful evaluation of these simple tests appears to have diagnostic utility in Cushing's syndrome.

REFERENCES

1. **Albright, F., Parson, W.,** and **Bloomberg, E.:** J. Clin. Endocrinol., **1,** 375, 1941.
2. **Cope, O.,** and **Raker, J. W.:** New England J. Med., **253,** 119, 165, 1955.
3. **Crooke, A. C.:** J. Path. & Bact., **41,** 339, 1935.
4. **Cushing, H.:** Bull. Johns Hopkins Hosp., **50,** 137, 1932.
5. Idem: J. Am. Med. Assn., **99,** 281, 1932.

6. Idem: Arch. Int. Med., **51**, 489, 1933.
7. **DeLaBalze, F. A., Reifenstein, E. C.,** and **Albright, F.**: J. Clin. Endocrinol., **6**, 312, 1946.
8. **Dougherty, T. F.,** and **White, A.**: Endocrinology, **35**, 1, 1944.
9. **Eisenhardt, L.,** and **Thompson, K. W.**: Yale J. Biol. & Med., **11**, 507, 1939.
10. **Farber, J. E., Gustina, F. J.,** and **Postoloff, A. V.**: Am. J. Dis. Child., **65**, 593, 1943.
11. **Haymaker, W.,** and **Anderson, E.**: Internat. Clin., **4**, 244, 1938.
12. **Hills, A. G., Forsham, P. H.,** and **Finch, C. A.**: Blood, **3**, 755, 1948.
13. **Kepler, E. J.,** and **Keating, F. R.**: Arch. Int. Med., **68**, 1010, 1941.
14. **Knowlton, A. I.**: Bull. New York Acad. Med., **29**, 441, 1953.
15. **Kovach, R. D.,** and **Kyle, L. H.**: Am. J. Med., **24**, 981, 1958.
16. **Maher, J. F.,** and **Kyle, L. H.**: Unpublished data.
17. **Oppenheimer, B. S.,** and **Fishberg, A. M.**: Arch. Int. Med., **34**, 631, 1924.
18. **Oppenheimer, B. S.,** and **Silver, S.**: Tr. Assn. Am. Phys., **52**, 146, 1937.
19. **Plotz, C. M., Knowlton, A. I.,** and **Ragan, C.**: Am. J. Med., **13**, 597, 1952.
20. **Randolph, T. G.**: Proc. Soc. Exper. Biol. & Med., **52**, 20, 1943.
21. **Rowntree, L. G.,** and **Ball, R. G.**: Endocrinology, **17**, 263, 1933.
22. **Sossman, M. C.**: Am. J. Roentgenol., **62**, 1, 1949.
23. **Sprague, R. G., Power, M. H., Mason, H. L., Albert, A., Mathieson, D. R., Hench, P. S., Kendall, E. C., Slocumb, C. H.,** and **Polley, H. F.**: Arch. Int. Med., **85**, 199, 1950.
24. **Walters, W., Wilder, R. M.,** and **Kepler, E. J.**: Ann. Surg., **100**, 670, 1934.
25. **Wang, C. C.,** and **Robbins, L. L.**: Radiology, **67**, 17, 1956.
26. **White, A.,** and **Dougherty, T. F.**: Endocrinology, **36**, 16, 1945.

SUMMARIO IN INTERLINGUA

Le Valor De Simple Studios Laboratorial In Le Diagnose Del Syndrome De Cushing

Le valor de simple studios laboratorial como adjuncto al diagnose del syndrome de Cushing esseva evalutate in 20 patientes. Leucocytosis polymorphonucleari e eosinopenia de grados significative esseva observate in un medietate del casos, e frappante augmentos del hematocrite esseva vidite in 25%. Un o plures de iste anormalitates hematologic esseva presente in 70% del casos.

Osteoporosis de grado moderate o marcate occurreva in 12 del 20 patientes, e le mesme numero habeva hypertension. Diabete patente o non-toleration de hydrato de carbon esseva presente in un levemente plus grande numero. Ex le total del anormalitates possibile, 2 o plus esseva presente in 19 patientes. Le numero medie del anormalitates apparente esseva 3.

Le meticulose evalutation de iste simple tests pare esser de utilitate diagnostic in casos de syndrome de Cushing.

PORTAL HYPERTENSION WITH ESOPHAGEAL VARICES IN ACUTE INFECTIOUS HEPATITIS: FURTHER OBSERVATIONS

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and

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During the course of earlier experiences with telescopic esophagoscopy, it was found that esophageal varices occur in some patients during acute viral hepatitis (Palmer and Brick[1,2]). The varices were regularly observed to be narrow, only occasionally measuring more than 3 mm. in diameter, and they were characterized by rather straight, even, branched courses. Attempts at measuring intravariceal pressure by transesophagoscopic needle puncture were at that time unsuccessful; it is very difficult to obtain clearly valid pressure readings from veins which are this small. The varices were not demonstrable roentgenologically, and no gastric varices could be recognized by gastroscopy. There was nothing to suggest that the varices had been responsible for bleeding.

Subsequently there appeared an important study by Reichman and Davis[3], showing by means of intrasplenic pulp-pressure studies that the portal pressure rises into the hypertensive range during the acute phase of viral hepatitis. Among 40 patients studied at the height of jaundice, the intrasplenic pressure was recorded as higher than 150 mm. of water in 18, and higher than 200 mm. in 7, the highest recording being 230 mm. (patient recumbent, zero-baseline taken as the level 4 cm. below the sternal angle; 20 or 22 gauge needle). During the convalescent period the highest pressure obtained on repeat measurement was 185 mm., and in 37 of the patients the pressure was 150 mm. or below. Twenty-three of the patients were examined esophagoscopically, from one to 21 days after the first pressure determination was made, but no esophageal varices were found. The type of esophagoscope used was not mentioned, and it is not known whether telescopic assistance was employed.

The present study was initiated because it was felt that more information is needed on the subject of portal hypertension and esophageal varices which are secondary to acute reversible liver disease, best exemplified by viral hepatitis.

Material and Method. Observations were made on 82 hospitalized patients with acute viral hepatitis and without other significant disease (cases previously reported are not included). They were all Caucasian men except for 3 Negro men and one Caucasian woman. The ages ranged from 18 to 47 years. The diagnosis of viral hepatitis was based on the usual historical, physical and laboratory findings. The hepatitis observed in these patients had its origin in Germany, France, Italy or Lebanon during the summer and fall of 1958. It was characterized generally by an unusually mild and brief subjective illness, but the objective changes could be classified as moderately severe. There were no instances of hepatic coma or other serious development. Liver biopsy specimens were taken in 40 cases, including all but 4 of those in which esophageal varices were found. All biopsies revealed the expected changes of viral hepatitis, without evidences of chronic liver disease.

The patients were examined esophagoscopically, following esophageal fluoroscopy, at intervals in their illness as indicated in the tables. The 53 × 9.5 Eder-Hufford esophagoscope, which is fitted with a telescope giving 4-diameter magnification, was used for all examinations. The patients were studied in the morning fasting state, following medication with 0.2 gm. of quick-acting barbiturate and 0.8 mg. of atropine. Observed varices were classified according to the length of the esophagus over which they coursed, the average diameter of the veins in the segment of esophagus most severely involved, and the venous pressure within the varices. Diameter was measured directly by a little ruler which is passed down the esophagoscope and laid against the vein, for reading under magnification. Pressure was measured by transesophagoscopic needle puncture of the varices, the balancing fluid being 0.9% aqueous saline solution and the zero-baseline being the axis of the esophagus (patient lying flat in the left lateral position; 22 gauge 2 cm. needle; shaft with 1 mm. bore).

TABLE 1.—PRESENCE OF ESOPHAGEAL VARICES IN RELATION TO DURATION OF THE HEPATITIS

Time Lapse Following Initial Symptom, Weeks	*Varices First Examination*		*Varices, Second Examination*			
	Present	*Absent*	*No. Patients with Varices Examined Again*	*Varices Disappeared*	*Varices Improved*	*Varices Unchanged or Worse*
1	1	1	–	–	–	–
2	6	9	–	–	–	–
3	11	17	–	–	–	–
4	6	6	2	–	–	2
5	3	0	8	2	1	5
6	4	3	4	3	1	–
7	1	0	1	–	–	1
8	0	1	4	3	1	–
10	1	1	4	2	–	2
12	1	1	1	–	–	1
14	–	–	1	–	–	1
16	1	1	–	–	–	–
24	0	2	–	–	–	–
29	0	1	–	–	–	–
32	0	2	–	–	–	–
36	0	2	–	–	–	–

Results. Esophageal varices were found in 35 patients, as shown in relationship to the duration of illness in Table 1. They were observed as early as one week after the onset of symptoms, and were present in 6 of 15 patients examined during the second week. Varices were found in half of the patients examined between the third and sixteenth week without decreasing incidence, but none was found after the sixteenth week.

The presence or absence of varices could not be correlated with the subjective complaints (Table 2), or with the objective stage of the illness (Table 3). Splenomegaly, which, except for varices, is the only possible indication of portal hypertension to be found in hepatitis patients, was present at the time of esophagoscopy in 17% of the patients who had varices and 12% of those who did not. The incidence of varices was approximately the same among patients who were examined after jaundice had recently cleared as it was among those still jaundiced. In several instances the varices were the last physical abnormality to disappear. The persistence of varices was

shown in another way, through repeat esophagoscopic examinations carried out in 25 of the patients whose first examination revealed varices (Table 1). The second examination was made from 1½ to 9 weeks after the first (1½ weeks, 6 cases; 2 weeks, 5 cases; 3 weeks, 4; 3½ weeks, 3; 4 weeks, 4; 7 weeks, 1; 8 weeks, 1; 9 weeks, 1), with disappearance of the varices in only 10 cases.

TABLE 2.—PRESENCE OF VARICES IN RELATION TO PATIENT'S SUBJECTIVE FEELINGS AT TIME OF ESOPHAGOSCOPY EXAMINATION

	No. Patients	*No. with Varices*
Height of subjective illness	9	4
Improving	20	8
Subjectively well	53	23

TABLE 3.—PRESENCE OF VARICES IN RELATION TO OBJECTIVE STAGE OF THE ILLNESS

	No. Patients	*No. with Varices*
Overt jaundice	46	24
Jaundice cleared, hepatomegaly and tenderness improving, etc.	15	6
No objective abnormalities except perhaps flocculation tests, BSP	21	5

The varices in all instances were of narrow caliber but they extended over rather long portions of the esophagus. The average diameter of the veins in the segment most severely involved averaged 0.5 mm. in 8 patients, 1 mm. in 9, 2 mm. in 15, and 3 mm. in 3. The varices regularly began at the region of the esophagogastric junction and extended orally variable distances: one-quarter the length of the esophagus in 9 cases, one-third in 11, one-half in 7, two-thirds in 5, three-quarters in 1, and 100% in 2. There was almost no tortuosity of the veins. The characteristic picture was that of smooth, even lengths of freely branching narrow veins which raised the mucosa in an obvious and clear-cut fashion. Roentgenologic examination succeeded in demonstration of varices in only 2 patients.

Portal venous pressures believed to be valid were obtained from the varices of 11 patients (Table 4). The level of portal hypertension was not striking, the highest reading being 300 mm. of saline solution (normal upper limit in fasting state, about 160 mm.; maximum observed in cirrhosis, about 640 mm.). The duration of the hepatitis had no obvious influence over the pressure.

During the course of illness, none of the patients had recognized bleeding from varices or any other source.

Discussion. Study of portal hypertension during acute liver disease, especially during active viral hepatitis, seems especially important for eventual elucidation of the natural history of esophageal varices. It has been assumed, for instance, that a long-standing head of portal hypertension is required before the tiny native portacaval

TABLE 4.—PORTAL PRESSURE WITHIN THE VARICES OF 11 PATIENTS, IN RELATION TO THE DURATION OF THE HEPATITIS

Time Lapse Following Initial Symptom, Weeks	*Pressures, mm. of Saline Solution*					
	150-180	*220*	*230-240*	*250-260*	*270-280*	*300*
2	–	–	2	–	–	–
3	–	–	–	2	1	–
4	–	1	–	1	1	–
5	1	–	–	–	–	–
6	1	–	–	–	–	–
9	–	–	–	–	–	1

venous connections across the cardia will open up, to become available for drainage of the portal system. It is apparent, however, that these natural venous shunts are almost immediately available for excessive portal demands.

It is necessary for the moment to assume that the explanation for portal hypertension during the course of viral hepatitis is simply interference with portal flow through the liver by the diseased organ's increased intra- and extracellular fluid content. There seems to be no reason at present to suppose that alteration in the arterial hemodynamics within the liver plays a part. That the cause for portal hypertension persists for a short while after clinical cure has been achieved is apparent, and in this connection it is interesting that no relation could be found between the presence or absence of varices and the apparent size of the liver. The same lack of correlation is observed in the portal hypertension of portal cirrhosis and of schistosomal liver disease.

There can be no question but that much of the discrepancy noted among reports on the incidence of varices in various diseases is due to differing criteria of just what constitutes a varix. As far as esophagoscopic recognition is concerned, considerable experience has taught that any vein which elevates the esophageal mucosa when the patient is breathing quietly is abnormal, almost always carries a head of pressure which is abnormally high for the portal system, and, therefore, must be considered a varix. There are, it is true, rare instances of esophageal varices in the absence of venous hypertension, truly idiopathic varices, but, unless the pressure is measured transesophagoscopically within the varix itself, such cases cannot be recognized.

Summary. Eighty-two (82) patients with viral hepatitis were examined by telescopic esophagoscopy in a study of portal hypertension as a manifestation of the disease. Half of the patients examined between the first week of illness and as long as other physical evidences of disease still persisted had esophageal varices. Varices persisted longer than other physical abnormalities. All of the veins were of narrow diameter and tended to have long straight, even courses. Portal venous pressure, as measured by needling of varices, was moderately elevated, the mean of 11 cases being 250 mm. of saline solution. No variceal bleeding was recognized in the group.

REFERENCES

1. **Palmer, E. D.,** and **Brick, I. B.:** Am. J. Med., **17**, 641, 1954.
2. Iidem: J. Am. Geriatrics Soc., **3**, 681, 1955.
3. **Reichman, S.,** and **Davis, W. D., Jr.:** Gastroenterology, **33**, 609, 1957.

SUMMARIO IN INTERLINGUA

Hypertension Portal Con Varices Esophagee In Acute Hepatitis Infectiose: Observationes Additional

Octanta-duo patientes con hepatitis virusal esseva examinate per esophagoscopia telescopic in un studio de hypertension portal como un manifestation del morbo. Un medietate del patientes examinate inter le prime septimana del morbo e usque al disparition de altere evidente signos del morbo habeva varices esophagee. Le varices persisteva plus longemente que le altere anormalitates physic. Omne le venas habeva diametros restringite e tendeva a sequer cursos longe e directe. Le tension porto-venose, mesurate per aguliation de varices, esseva levemente elevate. Le valor medie de 11 casos esseva 250 mm de solution salin. Nulle sanguination de varices esseva observate in le patientes de iste gruppo.

THE ROLE OF THE HIGHER BONDED UNSATURATED FATTY ACIDS IN NUTRITION AND HEALTH: A PRELIMINARY REPORT

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In this preliminary report, we wish to present a summary based upon approximately one quarter of a millon whole blood chemical assays, covering over 25,000 individual patients suffering from a rather wide variety of clinical disturbances.

We hope to establish the overall value and significance of such thorough nutritional assays in the diagnosis and treatment of these patients, particularly in such conditions as allergies, infantile asthma and eczema, hypercholesteremia, atherosclerosis, and especially coronary disease, pregnancy, habitual abortion, sterility, tensions of many different etiologies, mental retardation, including mongolism, the several types of arthritis, as well as various other less frequently encountered abnormal states. Individual reports covering each of the above mentioned conditions are in preparation and will be published as rapidly as they are completed.

In this report we shall attempt to emphasize the importance and we might reasonably say the necessity of examining the entire biochemical profile as obtained from whole blood under normal living conditions, rather than putting reliance on any individual component determination under artificial conditions such as fasting. Such fasting values, we have found, often are so confusing and misleading as to render them of relatively little practical value except for specific data on some given point.

Essentially, the assay which we are discussing relates to the physiologic balance of the more important nutritional factors as determined by their relationship to one another in whole blood samples, drawn at any time of the day without particular regard to food intake. These analyses, covering the major vitamin, mineral, and lipid components, are all performed upon the same sample of blood and thus reflect a composite picture of the patient's chemistry at any single given moment. This concept is in contrast to the many samples taken for single determinations of individual factors at different times, or even on different days, which obviously cannot be comparable.

Modern technologic advances in ultramicro methods and in the use of spectrophotometric procedures give us far more accurate and reproducible results than the older macrochemical techniques. This can be demonstrated most clearly by split specimens examined by different laboratories using different techniques, in which reports of individual substances have been found to vary by as much as 200%. On the other hand, the micro- and spectrophotometric methods performed in

duplicate or even in triplicate rarely vary more than a negligible 5 or 10%, which is well within the limits of experimental error.

Over a period of more than 10 years, we have learned that these complete assays present certain patterns which are so regular in occurrence that they can be used as supplementary diagnostic criteria in differentiating various clinical conditions.

There is one finding which is consistently observed in practically every case of such disturbed nutritional physiologic balance, representing the majority of the cases mentioned above, namely a lowered unsaturated fatty acid content of the blood, especially of the higher bonded types. It is our belief that these unsaturated fatty acid determinations are equally, if not more important than blood sugar or nonprotein nitrogen determinations as a routine laboratory procedure. Certainly the incidence of low levels of unsaturated fatty acids in the population at large is far greater than the incidence of hyperglycemia or of abnormal nitrogen levels in the blood.

Whether such deficiencies are the result of genetic influences, of infection, of allergy, of dietary abnormalities, of stress, or any one of many other causes, the fact remains that correcting this single defect in metabolism results almost regularly in some degree of clinical improvement. However, the role of the unsaturated fatty acids is only that of a single component of a much more complex interrelated disturbed nutritional metabolic relationship, and it is in examining these patterns as a whole that we are able to draw certain conclusions as to the nature of the underlying pathologic process, and to recommend means of treating the individual to overcome his deficiencies. But we hasten to add that not infrequently, several conditions may co-exist clinically with resultant initial confusion in respect to the interpretation of the biochemical profile. For example, a man with marked hypercholesteremia and hypertension may suffer also from certain allergies, and being in a position of heavy responsibility may be under severe stress at the same time. Under such lowered resistance, it is not unlikely to find that he may also be subject to repeated bouts of upper respiratory infection. This may be evidenced by additional depletion of both tissue and blood vitamins, minerals and fatty acids. The administration of a stable mixture of di-, tri, tetra-, penta- and hexaenoic fatty acids in proper proportion along with large doses of the specifically deficient vitamins and minerals will usually resolve the assay profile after 2 to 3 weeks' therapy, to a point where a fairly characteristic picture of the basic, underlying nutritional problem emerges.

More and more, we are beginning to recognize the importance and even the essentiality of these higher bonded unsaturated fatty acids, in relationship to our nutritional requirements, generally, and in relationship to fat metabolism and vitamin and mineral utilization, in particular. Brown[1] has recently emphasized the importance of the large amount of higher bonded fatty acids in mothers' milk as compared to the amount found in cows' milk, and suggests that no artificial formula should be recommended without supplying this fatty acid deficit.

In over 1200 cases of infantile eczema and asthma (Worne and Silbert[5,6], Worne and Smith[8]), prompt, dramatic relief of symptoms has been demonstrated repeatedly, usually within a matter of a few hours, by administration of a combination of such a stabilized fatty acid preparation as mentioned above, along with the necessary vitamin supplements. The same favor-

able clinical response is observed in many of the allergic problems found in infants and younger children (Worne and Silbert[7]). Years of study of dogs, cats, mink, fox, and chinchilla with poor coats, skin eruptions, chronic otitis externa and various other cutaneous problems have invariably shown low fatty acid blood levels on assay, the result of deficient dietary regimens. By corollary, there have been extremely rare clinical failures in these animals, when the proper fatty acid vitamin mixtures have been added to the feed, for a period of a few weeks.

No attempt will be made to discuss the problem of nutrition as a whole, in this report, but, simply, to emphasize certain phases as they apply to the various deficiencies which we constantly encounter. We all recognize that the income level of our population, as a whole, is tremendously high and that with more dollars in his pocket, the average citizen is eating more of everything, but especially of fats, up to as much as 40% or more of his total caloric intake. Most of these fats are fairly well saturated so that the ratio of unsaturated to saturated fats is unphysiologic. The evidence is rapidly accumulating that such a situation is bound to result in obesity and is associated with a very much higher rate of atherosclerosis than in a population in which the fats are less than half this figure and largely in the form of vegetable fats with a much lower degree of saturation.

Then too, as Hickman[2] has so ably demonstrated, man is a rather perverse animal, and with no economic restrictions, he shows no discretion in his choice of food, tending to eat an oxidative type of diet, high in carbohydrates and pre-oxidized fats, all of which tend to hasten oxidative activity and the development of high cholesterol levels and atherosclerosis.

We cannot avoid the conclusion that modern refining, processing and freezing of food, along with the problems of their transportation and storage, has modified the vitamin content of many of them. This is evidenced by the required fortification of such products as white bread and even milk. Unfortunately, such fortification is aimed at only one or two agents and does not reconstitute the product as a whole to its former state. This is not said to depreciate modern food processing, but simply to give recognition to the usually unsuspected "hidden hunger" which De Kruif so ably described many years ago, and to emphasize the need of individually tailored supplementation. The fact remains that these deficiencies do exist, and as long as they exist, we shall have clinical or subclinical symptoms of this or that deficiency syndrome. Most of these symptoms fortunately or unfortunately are compensated for to variable degrees, so that their nature is frequently not recognized or even suspected over a long period of time, unless the physician is alert to the problem. Such nutritional deficiencies are rarely lethal except in extreme cases, due to the amazing adaptation mechanisms of the body, but they do lead to subnormal functional activity, notably in the infant and in the geriatric patient, although no age can be considered exempt.

Is it any wonder that we have a vicious cycle? How can a woman with fatty acid deficiency be expected to deliver a completely biochemically normal child? Even if such a mother nurses her baby, her milk rarely has the fatty acid concentration which the child needs, and more often than not, the child, already deficient in fatty acids, is put on a cows' milk formula which contains a negligible amount of these essential substances. Is it sur-

prising that his metabolism is distorted and that various disturbances result, ranging from mild allergic reactions to severe bronchial asthma and eczema, and in some cases even to the point of mental retardation? We are oversimplifying the problem by these broad generalizations, but in essence, they are true. Successive pregnancies exhausting the mothers' reserves, or multiple generations of deficient individuals coupled with concomitant fetal cerebral anoxia lead to some of these extreme clinical pictures among which we believe mongolism and the vast majority of congenital defects can be attributed.

Our justification for such extreme statements is not based on any imaginative flights of fancy, but on hard, incontrovertible (in our opinion) experimental data. It has been shown repeatedly in animal experiments that interference with their oxygen supply or nutritional schedule at specific time intervals during gestation will result in rather characteristic deformities involving skin, skeleton and brain (Ingalls and Philbrook[3]). On the basis of both blood and urine assays of pregnant women, in our hands, it has been possible to prophesy with surprising accuracy whether or not the pregnancy will proceed normally, or terminate abnormally, even whether some congenital abnormality might be anticipated.

It is our belief that if therapy can be started at the earliest recognized moment of pregnancy, and the blood levels of the essential higher bonded fatty acids, along with the associated deficient vitamins and minerals, as well as the hormones, are maintained, the pregnancy will be normal and the baby almost certainly will be born without congenital defects. It is our further contention that if the baby is breast fed by this normal mother, or if his formula is supplemented to maintain his fatty acid blood levels, the incidence of asthma, eczema or any of the usual infant and childhood allergies will be markedly reduced, as long as these levels are maintained. Let us not forget that the results of these deficiencies may well be cumulative in successive generations, therefore, it is not surprising that allergies and infantile asthma are increasing at an alarming rate. With such deficient physiologic mechanisms transmitted, and perpetuated by our lowered mortality rates through control of infectious diseases, especially during childhood, we are getting further and further from the concept of the survival of the fittest. Indeed, we are, in effect, following exactly the diametrically opposite course of that which we follow in improving our animal stock by breeding out defective traits. Obviously, man is too complicated an organism combining emotionalism with his biology, as he does, to be willing to be an experimental subject. Nor have we any scientists of sufficient longevity to carry out such experiments over more than parts of two generations.

Accordingly, we have to assess our data on the basis of clinical effect, and regulate our specific therapy according to the individual response. In this respect, treatment becomes a highly specialized procedure, just as is true in the case of diabetes or hyperthyroidism. It involves a thorough knowledge of physiologic mechanisms, based on biologic chemical reactions, and the application of that knowledge to solving the patient's particular problem. There are no "miracle" or "wonder" drugs in nutrition, at least not in the sense that the newer antibacterial agents have had such properties attributed to them. Yet, used properly and intelligently, they are miracle agents in restoring to a substantial degree physiologic balance in many

cases, and physiologic balance very properly can be defined as what we commonly call good health.

It is impossible, within the time limits of such a presentation, to attempt to cover but a very small segment of the nutritional problems which these studies represent. Let us merely hope that our investigational approach and the encouraging results which we have obtained will stimulate others in the general field of nutrition to explore the possibilities of this many-pronged attack upon some of the remaining challenges of medicine, especially the mental disease problem; not only the obvious developmental defects and abnormalities, but many of the so-called "functional" disturbances ranging from various stress phenomena to outright psychosis.

Chemopsychiatry or pharmacopsychiatry are terms with which we are all becoming more and more familiar. It is our belief that these "functional" conditions almost invariably have an abnormal metabolic background, which the multiple assay profile type of study can frequently detect. Biochemical knowledge of nervous system physiology when applied properly, we are convinced, will result in the ability to correct the existent deficiency as the first step towards effecting the patient's recovery. Whatever the alteration involves, whether phospholipid ratios, enzymatic blocking, mineral deficiency, or any one or more of many other things, these material substances can be provided. However, in addition, the help of a psychologist, or, in more severe disturbances, the psychiatrist makes up the second stage of therapy. We see the necessity of these combined forces to attain the best results in almost every mental case, whether it is a mongol, a retarded or emotionally disturbed child, an adult having difficulty coping with an emotional stress problem or a frank schizophrenic personality. At this point we can only say that the results obtained by the combined efforts of the various members of our research team have been more than encouraging and are deserving of much more widespread investigation.

In geriatrics, the literature is replete with references to the nutritional requirements of the older individual. Vitamin and mineral supplements are recognized as being, for all practical purposes, necessities. Great diversity of opinion exists as to the protein requirements, with especial interest today being centered on specific amino acids. Fats, likewise, offer a problem on which no agreement exists. Shall they be animal fats or vegetable fats? What percentage of the total diet should they represent? But only rarely does anyone bring up the matter of the unsaturated fatty acids and almost never a suggestion as to their proper ratio to secure optimal utilization of the other components.

Again, in our experience with patients in their seventies and eighties, it is rare to find a "normal" total nutritional assay of the type we have described. Almost invariably, the blood unsaturated fatty acids are low as are certain selected vitamins and minerals. The sodium-potassium ratio is often reversed as is that of the phospholipids and cholesterol. Most of these patients, at least the ones we see after everyone else has thrown up their hands, are real problems. They are often depressed, worried, unhappy, suffer from arthritis or "rheumatism," have no appetite, are constipated, don't sleep well, are irritable, and frequently their mind wanders or they sit motionless in an almost vegetative state. Correcting their blood and tissue chemistry, even if only partially, and giving them encouragement, including often actual psychologic therapy will put many of these

older citizens back to the point where they have an interest in living, where they become part of their community, where they can get perhaps to the movies or to dinner once in a while, where they enjoy their food, sleep well and are no longer serious custodial problems. True, they are still their chronologic age, but their physiologic age has become modified to match their actual years; they are happy, leading more or less useful, purposeful lives again. Unsaturated fatty acids are not the whole story, but they are a key which we believe will help unlock many of the doors of our presently unexplored areas of nutrition.

While we are in this area of advanced years, it brings us to another almost common problem, and one of intense, and at times, almost bitter controversy. This is the question of elevated blood cholesterol levels and their relationship to atherosclerosis in general (cerebral, peripheral) but to coronary disease, in particular. Suffice it to say at this point, in this brief outline of fatty acid deficiency syndromes, that it is, indeed, a rare case of elevated cholesterol in which we find a normal unsaturated fatty acid level. We do not intend to tilt our lance at the significance of high blood cholesterol levels as they apply to the individual case. We can state with complete confidence, however, that in cases of high blood cholesterol and low unsaturated fatty acid blood levels, the cholesterol can be reduced without significantly having to modify the average diet by building up the blood level of the higher bonded unsaturates. This can be accomplished more promptly by adding 50 to 100 mg. of Niacin (not nicotinamide) to the gram or more of a proper fatty acid mixture given three or four times a day. In our opinion, the statistical evidence of a lowered incidence of coronary disease in individuals with average cholesterol levels and normal average phospholipid-cholesterol ratios as compared with the incidence of coronary disease in people of the same general age and social circumstances with high cholesterol levels would suggest that it is preferable to belong to the former group. When it is so simple to accomplish this desirable state without rigid dietary restriction, it would seem only common sense to do so. Additional data on racial differences, dependent largely upon dietary intake, of blood cholesterol levels and coronary disease only serves to strengthen the hypothesis that a reasonably average cholesterol level is something to strive for.

Summary. We have touched briefly upon the importance of the higher bonded fatty acids in nutrition and health generally. We have outlined a few of the more outstanding clinical examples resulting from their deficiency, and indicated how by a proper nutritional assay it is possible to correct to a very great extent these deficiencies. Obviously, the problems have been oversimplified for the sake of brevity and emphasis, but a discussion of the data on literally thousands of cases including infantile asthma and eczema, other skin conditions, allergies, generally, but especially those of childhood, mental health, geriatric problems and atherosclerosis has been presented with the objective of arousing interest in the biochemical and metabolic approach to nutrition as controlled by routine quantitative assay of the essential lipid, vitamin and mineral levels of the individual's whole blood, rather than by a caloric-intake estimation. This latter gives us no information as to the actual amounts of essential dietary supplements present in the food, nor of any metabolic defects of the individual in respect to absorption and utilization of such agents needed

for the maintenance of true nutritional health. While it is true that detailed knowledge of the mechanisms involved in the role of the higher bonded unsaturated fatty acids in metabolism is still far from complete, studies by nutritionists and biochemists all over the world have recognized in recent years their vital importance in maintaining a healthy body economy.

As Williams states, "people are individually different from one another, the result of inherited qualities which can often be explained and quite possibly corrected by attention to the specific nutritional requirements of the particular individual" (Williams[4]). This genetotrophic approach deserves much more widespread recognition by the medical profession than it has received up to the present, for the physician must treat the individual, as well as the particular disease from which he happens at the moment to be suffering.

REFERENCES

1. **Brown, J. B.:** Fundamental Considerations in the Selection of the Fatty Acid Composition of the Diet in Infancy, and Vitamin B_6 in Human Nutrition. Report of the Tenth M & R Pediatric Research Conference, Columbus, Ohio; M. & R Laboratories, 1954.
2. **Hickman, K.:** Biologic Antioxidants. Fourth Conference. New York: Josiah Macy, Jr. Foundation, p. 114, 1949.
3. **Ingalls, T. H.,** and **Philbrook, F. R.:** New England Med. J.. **259,** 558, 1958.
4. **Williams, R. J.:** Nutrition and Alcoholism. Oklahoma City: University of Oklahoma Press, 1951.
5. **Worne, H. E.,** and **Silbert, N. E.:** Vitamin Deficiency and Blood Chemistry Patterns in the Asthmatic State. Third Internat. Congress on Diseases of the Chest of the American College of Chest Physicians, Barcelona, Spain, October, 1954.
6. Iidem: A Preliminary Report on the Circulating Blood Levels of Certain Metabolites in Bronchial Asthma. Third Internat. Congress on Broncho-esophagology, Lisbon, Portugal, October 12, 1954.
7. Iidem: Arch. Research, **1,** 16, 1954.
8. **Worne, H. E.,** and **Smith, L. W.:** The Biochemistry of the Blood in Bronchial Asthma. Fifth Internat. Congress on Bronchoesophagology, Vienna, Austria, August 31, 1956.

SUMMARIO IN INTERLINGUA

Le Rolo Del Polyenoic Nonsaturate Acidos Grasse In Nutrition E Sanitate: Reporto Preliminar

Nos ha commentate brevemente le importantia del polyenoic acidos grasse in nutrition e sanitate in general. Nos ha delineate certes del plus prominente consequentias clinic de deficientias in ille compositos e ha indicate como il es possibile, super le base de un appropriate essayage nutritional, corriger tal deficientias usque a certe sed significative grados. Evidentemente, le problemas ha essite simplificate excessivemente in le interesse de brevitate e emphase, sed un discussion del datos ab litteralmente millenas de casos—incluse casos de infantil asthma e eczema, de altere conditiones cutanee, e de allergias in general e specialmente de casos representative de problemas pediatric, psychohygienic, e geriatric e de atherosclerosis—es presentate con le objectivo de stimular le interesse pro methodologias biochimic e metabolic in studios nutritional, ubi le conclusiones es supportate per un routinari essayage quantitative del nivellos de essential lipidos, vitaminas, e minerales in le sanguine integre del individuo plus tosto que per estimationes del ingestion caloric. Datos de iste ultime

genere—*i.e.* datos concernente le ingestion caloric—provide nulle information super le ver quantitates del essential supplementos dietari que es presente in le alimentos o super le defectos metabolic del individuo con respecto al absorption e utilisation del agentes biochimic que es necessari pro mantener un ver sanitate nutritional. Il es ver, nostre comprension del detalios del mechanismos per que le polyenoic nonsaturate acidos grasse exerce lor functiones metabolic es extrememente incomplete, sed nutritiologos e biochimistas in omne partes del mundo ha recognoscite in recente annos le importantia vital de ille substantias pro le mantenentia de un salubre economia del corpore.

Como Williams lo exprime, "le gente differe individualmente in consequentia de qualitates geneticamente determinate que es frequentemente explicabile e mesmo corrigibile per attention prestate al specific requirimentos dietari del individuo in question."[4] Iste conception genetotrophic merita un plus extense recognition del parte del profession medical que illo ha recipite in le passato, proque le medico debe tractar le individuo e non solmente le maladia de que le individuo suffre a un momento particular.

AN EARLY, HITHERTO UNRECOGNIZED, SIMPLE ROENTGENOGRAPHIC AID IN THE DIAGNOSIS OF MAJOR PULMONARY EMBOLISM*

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Pulmonary embolism may be difficult to recognize. A suggestive history leads to electrocardiographic and roentgenographic studies. The electrocardiogram may be characteristic or more commonly equivocal or nonspecific. Pulmonary parenchymal densities compatible with infarction support or establish the diagnosis. But pulmonary infarction does not always follow pulmonary embolism, particularly when the embolus involves the major branches of the pulmonary artery (Hampton and Castleman[1], Owen *et al.*[2]). Such an embolus may be manifested roentgenographically by radiolucency of the affected portion of lung (Westermark[4]). More commonly, no abnormality of the pulmonary artery or parenchyma is discernible. Indeed, the negative chest roentgenogram may sway the physician away from the diagnosis of pulmonary embolism. Yet, it is this very type which is most dangerous, and, if untreated, can be fatal or produce at a later time chronic cor pulmonale (Owen *et al.*[2]).

Case Report. Mrs. J. R., 56 years old, was admitted to Temple University Medical Center on December 29, 1957, for evaluation and treatment of gastric symptoms of 15 years' duration. The physical examination revealed normal findings. She was 50 inches tall and weighed 125 pounds. The blood pressure was 112 mm. mercury systolic and 75 mm. diastolic. Roentgenographic study of the chest disclosed normal findings (Fig. 1). Roentgenographic and gastroscopic studies of the stomach revealed findings consistent with polypoid adenomas. Electrocardiogram and laboratory studies were normal.

On January 16, 1958, surgery was performed and 2 gastric polypoid adenomas, confirmed histologically, were removed.

The postoperative course was uneventful until January 18, when she began to have a low grade fever without apparent cause. On January 21, although ambulant, she appeared drawn and depressed. On January 24, a focal area of "cellulitis" was noticed on the anterior aspect of the left leg. Homan's sign was not present. Because of suspicion of phlebitis, the legs were wrapped in elastic bandages. On January 26, at 9:30 A.M., she collapsed in the lavatory following a bowel movement. She recovered consciousness quickly but her skin was cold and clammy. The pulse rate was 110 per minute and the blood pressure 50 mm. systolic and 0 mm. diastolic. Norepinephrine was given intravenously and anticoagulant therapy with heparin was begun. Several hours later, clinical examination disclosed a precordial friction rub which was transient in duration. Serial electrocardiograms incited suspicion of myocardial infarction. Meanwhile, the blood pressure could be maintained only by norepinephrine. Portable roentgenogram of the chest on January 27 showed clear lung fields (Fig. 2). The cardiac silhouette was increased in size and its right border bulged. The mid-right

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diameter increased to 63 mm. from the control of 49 mm. Later, gradual improvement appeared to be occurring, although norepinephrine administration had to be continued. On January 31, she developed severe pain in the chest and again became cold and clammy. Portable roentgenogram of the chest now showed for the first time pulmonary elevated above the surrounding soft parenchyma. The small branches of the pulmonary artery within these areas were filled with thrombi. Examination of the heart revealed no abnormality other than minimal atherosclerosis of the aortic valve and coronary arteries. Chamber volume was not determined.

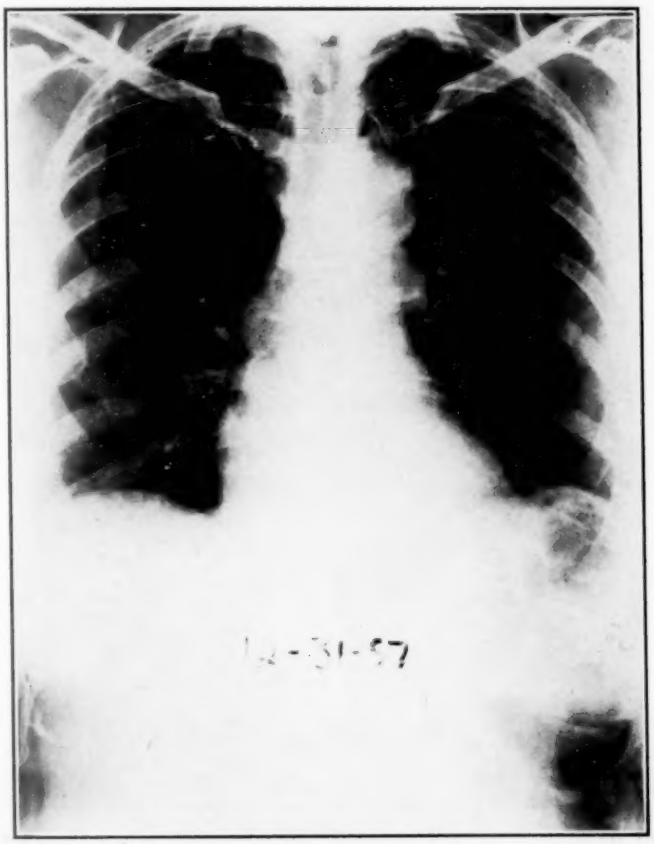

Fig. 1.—Normal chest roentgenogram on December 31, 1957. The Mr diameter of the cardiac silhouette is 49 mm.

parenchymal densities but of nonspecific type. She died at 4:55 A.M. on February 1, 1958.

At necropsy, the right pulmonary artery was filled with clot, white to gray in color and firmly adherent to the intima. Its secondary and tertiary branches also contained clots. The left pulmonary artery was free of clot. The lower lobe of each lung was deep purplish red in color, firm in consistency and slightly

Discussion. The mid-right (Mr) diameter of the cardiac silhouette is the greatest horizontal distance between the mid-spinal line and the right border of the cardiac silhouette in the frontal plane (Zdansky[5]). It rarely exceeds 50 mm. in the normal. In 50 con-

secutive randomly selected chest roentgenograms of normal adults, 16 to 70 years of age, the Mr diameter was 50 mm. or less in all but three (Soloff and Zatuchni[3]). Conversely, an Mr diameter greater than 50 mm. tends to be associated with an increased right atrial volume (Soloff and Zatuchni[3]). Of course, conditions other than right atrial enlargement may also increase the Mr diameter. These include rightward displacement of the cardiac silhouette, chest deformities, cardiac tumors, diaphragmatic herniae, adjacent pulmonary or pleural disease and most important pericardial disease. Hence, the interpretation of the meaning of an increased Mr diameter depends upon analysis of the circumstances under which such an increase occurs and also upon exclusion of conditions other than enlargement of the right atrium.

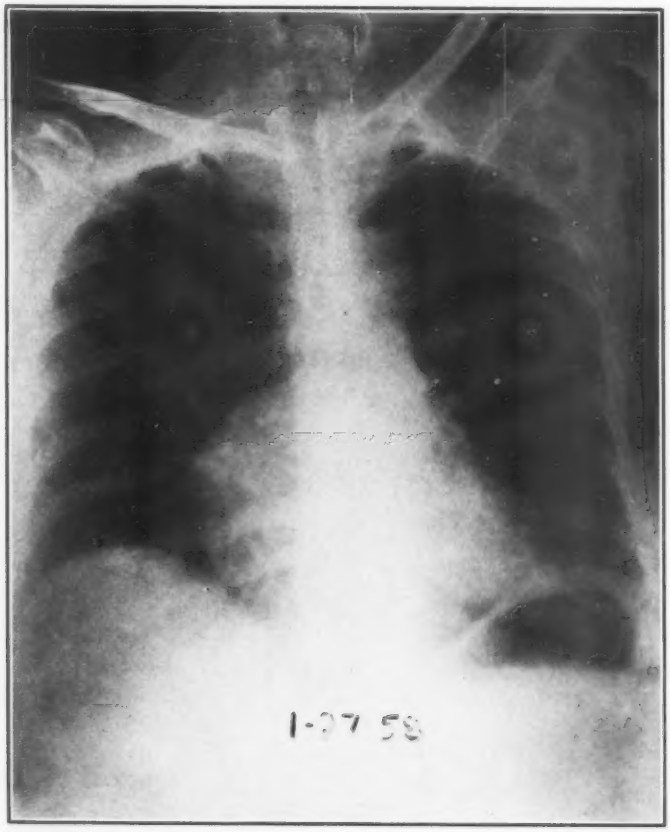

Fig. 2.—Chest roentgenogram on January 27, 1958, following the occurrence of pulmonary embolism. The lungs are clear. The cardiac silhouette has increased in size with disproportionate increase in its Mr diameter to 63 mm. and bulging of its right border.

The Mr diameter was normal in the chest roentgenogram taken upon admission into the hospital. After pulmonary embolism occurred, the Mr diameter greatly increased and the increase was far out of proportion to the distor-

tion produced by the portable roentgenographic study. Moreover, the right border of the cardiac silhouette became more convex and bulged to the right.

Pericardial effusion can also produce this roentgenographic finding which was supported by a pericardial friction rub. But the clinical picture combined with the electrocardiographic findings quickly dispelled this lesion as the dominant one. At necropsy, only 20 ml. of pericardial fluid were present.

Increase in the Mr diameter with bulging of the right border of the cardiac silhouette was initially the only roentgenographic change. This change tipped the scale in favor of interpreting the clinical features and the electrocardiographic abnormalities as due to pulmonary embolism.

Conclusion. An increase in the Mr diameter with bulging of the right border of the cardiac silhouette may be the sole initial roentgenographic finding of major pulmonary embolism.

REFERENCES

1. **Hampton, A. D.,** and **Castleman, B.:** Am. J. Roentgenol., **43,** 305, 1940.
2. **Owen, W. R., Thomas, W. A., Castleman, B.,** and **Bland, E. F.:** New England J. Med., **249,** 919, 1953.
3. **Soloff, L. A.,** and **Zatuchni, J.:** Unpublished observations.
4. **Westermark, N.:** Acta radiolog., **19,** 357, 1938.
5. **Zdansky, E.:** Roentgen Diagnosis of the Heart and Great Vessels. New York: Grune & Stratton, Inc., 1953.

SUMMARIO IN INTERLINGUA

Un Precoce, Usque Nunc Non Recognoscite, Simple Adjuta Roentgenographic In Le Diagnose De Major Embolismo Pulmonar

Un augmento del diametro centro-dextere con extrusion del margine dextere del silhouette cardiac pote esser le sol constatation roentgenographic initial in casos de major embolismo pulmonar.

A STUDY OF THE HUMAN TORSO AS A VOLUME CONDUCTOR BY COMPARATIVE VECTORGRAM ANALYSIS: THE dR FACTOR

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Despite certain problems imposed by the nature of the heart itself and the human body surrounding it, electrocardiography has proved to be a valuable diagnostic tool in clinical cardiology. Its value may be further enhanced if the true electrical activity of the heart can be accurately demonstrated from measurements recorded at the body surface. Accurate measurements depend upon the validity of the dipole concept and knowledge of the conductive properties of the body tissue between the heart and the surface point of measurement. A great deal of investigation by Burger and Van Milaan[1,2,3] has been done in clarifying the heart vector (dipole) concept and in evaluating the influence of phantom models upon conduction. These investigators used phantom models with artificial lungs, viscera and spinal column to evaluate the influence in lack of homogeneity. Later Frank[5,6] studied the influence of an eccentric dipole within a phantom model. These studies have provided much useful information.

The complexity of volume conductors appears to be a never ending dilemma. Recent attention has been directed to the image boundary concept which further complicates the problem (Nelson[8]). The unending complexities suggest that no artificially constructed volume conductor can escape the possibility that it is not a true representation of the characteristics of the human body. Moreover the use of a dipole within a torso model does not necessarily represent the electrical characteristics of the three dimensional heart. The purpose of this paper is to (1) set forth a simple method of evaluating the influence of distance and resistance (dR factor) between the heart and points on the surface of the human body for any subject; (2) evaluate the apparent validity of the dipole representation at various surface points on the body; (3) illustrate the changes in the dR factor expected as a normal biological variable. In evaluating this problem the comparative vectorgram technique of Hartman, Veyrat, Wyss and Duchosal[7] was found to be most useful. The application of this method is presented in a previous publication (Smith and Lamb[9]).

DEVELOPMENT OF EXPERIMENTAL HYPOTHESIS. The simple concept of dipole representation of the electrical activity of the heart is utilized as a starting point. A simple dipole acting at point E will cause potential difference between different points on the body surface and between surface points relative to point E.

The potential at a surface point (Vp) depends upon a geometric factor or the projection of the dipole vector (heart vector) on a line (d) drawn

from the surface point to E point and an electrical factor imposed by the resistance (R) of the conducting media between E point and the surface point. This may be expressed as an equation,

$$Vp = VE \times Cos\ \theta \times 1/R$$

where Vp equals the surface potential at point p, VE equals the dipole value at E, Cos θ is the cosine of the angle between the distance (d) and the dipole vector and R represents the resistance imposed by distance and electrical conductivity (Fig. 1).

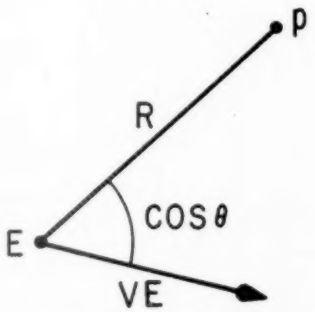


Fig. 1.—An illustration of the classic concept of the relation of potential at a distant point (p) to the potential at a point source (VE).

The dipole vector (VE) can be represented by its three mutually perpendicular components. These may be expressed as VE_x, VE_y, VE_z (Fig. 2). Each component vector contributes to the surface potential measurement at a given point p. The effect of the x, y, z, components at the surface point is designated Vpx, Vpy, Vpz. A series of equations may then be developed:

$$VE = \sqrt{VE_x^2 + VE_y^2 + VE_z^2}$$

$$Vpx = VEx \times Cos_x\ \theta \times 1/R$$

$$Vpy = VEy \times Cos_y\ \theta \times 1/R$$

$$Vpz = VEz \times Cos_z\ \theta \times 1/R$$

$$Vp = \sqrt{Vpx^2 + Vpy^2 + Vp_z^2}$$

Referring to Figure 2:

Cosine $_x\theta$ equals the cosine of the angle between VE_x and d.

Cosine $_y\theta$ equals the cosine of the angle between VE_y and d.

Cosine $_z\theta$ equals the cosine of the angle between VE_z and d.

Three mutually perpendicular coordinates parallel to the three mutually perpendicular component vectors may be projected from surface point *p*. These may be utilized to determine the geometric factors (heart vector projection). For purposes of identification in this discussion these coordinates will be designated X coordinate, Y coordinate and Z coordinate. The relation of any such coordinate to a parallel component vector of a dipole vector has been demonstrated by Duchosal and Sulzer[4] (1949). The angle between VE_x component and the distance (d) is equal to the angle between the d and X coordinate (opposite angle between parallel lines created by an intersecting line). Since the cosine of an angle equals the adjacent side divided by the hypotenuse, it follows:

Cosine of the angle between X coordinate and distance (d) = the geometric length of X coordinate/distance (d), and by substitution,

$$Cos_x\theta = LX/d$$

where d is the geometric length of the distance.

Similarly

$$Cos_y\theta = LY/d \text{ and}$$
$$Cos_z\theta = LZ/d$$

By substitution of LX/d for $Cos_x\theta$, Vp_x may be expressed:

$$Vpx = VE_x \times LX/d \times 1/R \text{ or}$$
$$Vpx = VE_x \times LX/dR$$

and similarly

$$Vpy = VEy \times LY/dR \text{ and}$$
$$Vpz = VEz \times LZ/dR.$$

For any given point in the calculation of Vpx, Vpy or Vpz *the dR factor is a constant* for all three above equations, while the VE components and the X, Y, Z coordinate lengths are variable.

roentgenographic examination (usually about the level of the fifth rib) and (3) that the resistance (R) between E point to a point above the Y_0 plane* corresponds to the resistance between E point and a similar point below the

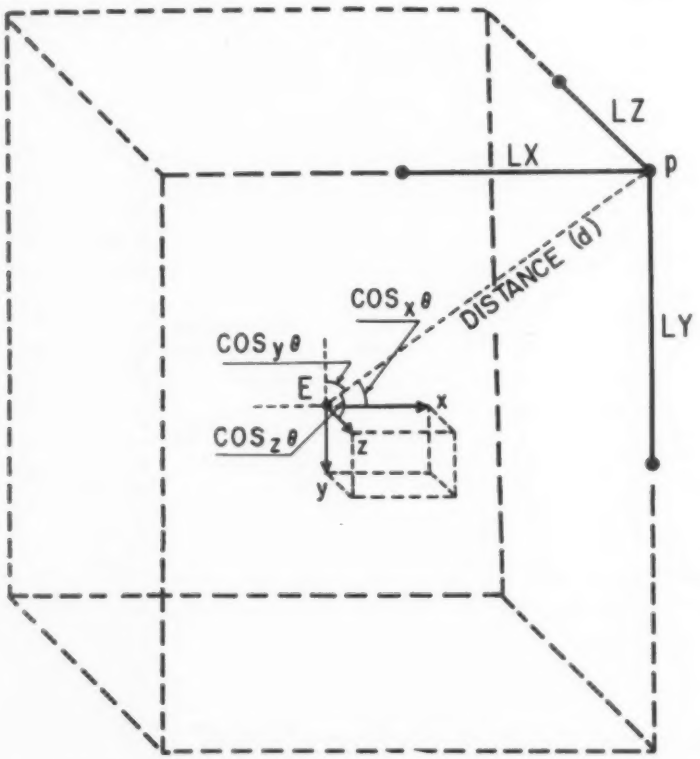


Fig. 2.—A geometric analysis of the influence of the X, Y, Z, components of a dipole vector on the potential at point p.

To set up a workable hypothesis for experimental evaluation it will be assumed (1) that the electrical activity of the heart may be represented as a dipole at more distant surface points; (2) that the vertical location of the E point can be located fairly well by Y_0 plane. If these assumptions are reasonably correct, given symmetrical points 1 and 1′ (Fig. 3), the value of Vp_x will be the same at both points and Vpz should be equal at both points. The value for Vpy should be equal at both points but opposite in

*The Y_0 plane designates the plane perpendicular to the Y component vector and located at its point of origin, point E. It is necessarily at the level of the point of origin for the X and Z component vectors. Theoretically and by vector analysis, points located on the Y_0 plane should have no value related to the magnitude of the Y component as all such points are perpendicular to the vertical vector component.

sign as point 1 is above and point 1′ below the Y_0 plane. Similar relations should exist between p2 and p2′, between p3 and p3′ and between p4 and p4′.

When potential difference is obtained by placing a negative electrode at p1 and a positive electrode at p1′ the value is related only to the Y component.* A relative value of only the Y component will be obtained when recording potential difference between any of the symmetrically paired points. All measurements from such bipolar leads should be similar throughout the cardiac electrical cycle, their only difference being in amplitude.

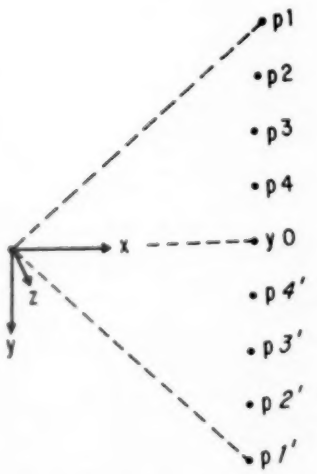


Fig. 3.—An illustration of the relative relationship of X, Y, Z, component vectors on symmetrical points above and below the Y_0 plane (see text).

When true lead similarity is demonstrated by recording a straight line vectorgram, the relative dR for the two dissimilar points (p1 and p2) can be calculated. Similarly when one bipolar lead is used as a reference lead and a second bipolar lead is used as an exploring lead the dR factor for all points may be expressed relative to the dR factor for the reference lead. To illustrate, with a bipolar reference lead attached at p1 and p1′ and an exploring bipolar lead attached at p2 and p2′ one can assume a dR factor of 1.00 for p1, then calculate as a decimal fraction the dR factor for p2. All other points used in subsequent comparative vectorgrams can also be expressed as decimal fractions of the dR factor for p1 or p1′. In such a manner the relative influence of distance and resistance between E point and a series of points on the body surface can be expressed. Such calculations are only valid when satisfactory lead similarity is demonstrated.

A simple formula has been derived to calculate the dR factor relative to two reference points, for example p1 or p1′. The only measurements required are: 1) the recorded potential difference for the reference lead (Vp1′ — Vp1), 2) the coordinate length of the reference lead (geometric distance between p1 and p1′), 3) the recorded potential difference for the exploring lead (for example, Vp2′ — Vp2) and 4) the coordinate length of the exploring lead (geometric length between p2 and p2′). All four of these values may be obtained from the recorded vectorgram or the human subject. The formula may be stated:

$$\frac{\text{L p2} - \text{p2}'}{(\text{Vp2}' - \text{Vp2})} \times \frac{(\text{Vp1}' - \text{Vp1})}{\text{Lp1} - \text{p1}'} = \text{dR factor for p2 or p2}'$$

expressed as a decimal fraction of the dR factor for p1.

*Since Y is the only one of the three components with an opposite sign at similar paired points it is added, whereas X and Z components are cancelled by the difference in lead polarity; for example,

$$+ (+ \text{X} + \text{Z} + \text{Y}) - (+ \text{X} + \text{Z} - \text{Y}) =$$
$$+ \text{X} + \text{Z} + \text{Y} - \text{X} - \text{Z} + \text{Y} = 2\text{Y}$$

In a hypothetical situation if the length between p1 and p1′ is 32 cm. and the maximum potential difference between the two points is 2.0 mv. while the length between p2 and p2′ is 24 cm. with a recorded potential difference of 1.6 mv., the calculation is simply

$$\frac{24 \text{ cm.}}{1.6 \text{ mv.}} \times \frac{2.0 \text{ mv.}}{32 \text{ cm.}} = 0.94.$$

Thus if the dR factor for p1 is 1.00 the dR factor for p2 is 0.94.

The derivation of the relative dR formula is presented as an appendix.

Experimental Method. When two different leads truly represent the measurement along the same coordinate their configuration and relative amplitudes will be the same in a synchronous fashion. Two similar wave forms may not be synchronous, creating linear graphs that give a false impression of true similarity. To avoid this error the comparative vectorgram technique of Hartmann, Veyrat, Wyss and Duchosal[7] (1955) was employed in this study. The use of this method as an experimental tool was demonstrated in a previous publication[9]. Utilizing the X and Y axis of the beam of a cathode ray oscilloscope, if the same lead is introduced into the X and Y input the beam will move across the screen in a straight line during the cardiac cycle, that is, the loop is completely closed, appearing as a straight line. The line will have an inclination of 45° when proper and equal amplification is used for both the Y and X axis. If the amplification is not equal for the X and Y oscilloscope axis, the angle of inclination for the line will not be 45°, although the loop remains a closed loop or straight line.

As developed in the preceding hypothesis a bipolar (Y) lead attached at p1 and p1′ measures an event similar to bipolar (Y) lead attached at p2 and p2′. By introducing lead Vp1′ — Vp1 into the X oscilloscope axis and lead Vp2′ — Vp2 into the Y oscilloscope axis their true similarity can be observed. A completely closed loop throughout the cardiac cycle confirms true similarity. True similarity presupposes correct electrical and geometric positioning above and below the Y_0 plane and confirms the validity of the dipole concept for those particular reference points as well as requiring a similar dR factor for comparable surface points (p1 and p1′, p2 and p2′, p3 and p3′, p4 and p4′).

Although the leads might be similar, differences in amplitude are to be expected between two such leads because of the difference in the LY value and dR factor for p1 compared to p2 or for p1 to p3. This difference in amplitude would be reflected in the change in inclination of the closed loop.

Failure to fulfill the above hypothesis in one or more of its assumptions should result in dissimilar leads recorded as a true loop (open loop) rather than a closed loop or straight line.

A routine 6 foot chest roentgenogram was utilized to estimate the level of E point or the Y_0 plane. In the subjects studied, the geometric center of the left ventricle was chosen and located most often at the level of the fifth rib about 4 cm. to the left of the mid-sternal line. This point was located on the subject's back and anterior thorax. An X and Y coordinate was drawn through this point on the back. A series of 56 points were then measured at 4 cm. distance from each other over the surface of the back. Twenty-eight points were above the Y_0 plane and 28 similar or prime points were located below the Y_0 plane (Fig. 4). A surface over the anterior chest wall was mapped out in a similar fashion, consisting of 28 points above the Y_0 plane and 28 similar points below the Y_0 plane.

A positive electrode was placed at p1′ (back) and a negative electrode was placed at p1 (back) for a reference or stationary lead. A second bipolar lead was used as the exploring or comparative lead. The exploring lead was located successfully at p2 and p2′, p3 and p3′, p4 and p4′, p5 and p5′ . . . p28 and p28′. During these determinations the subjects were lying face down. The subject was then reclined on his back with the original stationary electrodes remaining on the back at p1 and p1′ while the exploring lead was placed successively over the front at p1 (front) and p1′ . . . p28 and p28′. At least 3 photographs were taken of each comparative trial. The electrodes were square, being 2 cm. on each side.

Eighteen subjects were studied completely on one or more occasions. An additional 15 subjects were studied for a limited number of the points in evaluating the most promising locations used later for developing 3 mutually perpendicular orthogonal leads.

The Y lead axis was deliberately chosen as it appeared more accurate to measure the Y lead axis length from points above and be-

low the Y_0 plane. The natural curvature of the thorax distorts straight geometric relations of the X lead and of course the uncertainty of the anterior-posterior location of the E point makes the Z lead axis measurements even more uncertain.

After recording all comparative leads, the records were examined to determine their true similarity, judged by how nearly the vectorgrams appeared as a straight line. A straight line was taken to mean excellent similarity. Records from all points showing good similarity were then used to measure the maximum deflection in both the X and Y axis. The measured or observed value at each location was used to calculate the relative dR factor for each point. LY was measured for each point on the body and Vp′ — Vp was read directly from the film. Using p1′ -p1 as the reference lead the values were substituted in the final formula derived in the above experimental hypothesis and the dR factors for all points expressed relative the dR factor (1.00) for p1 and p1′.

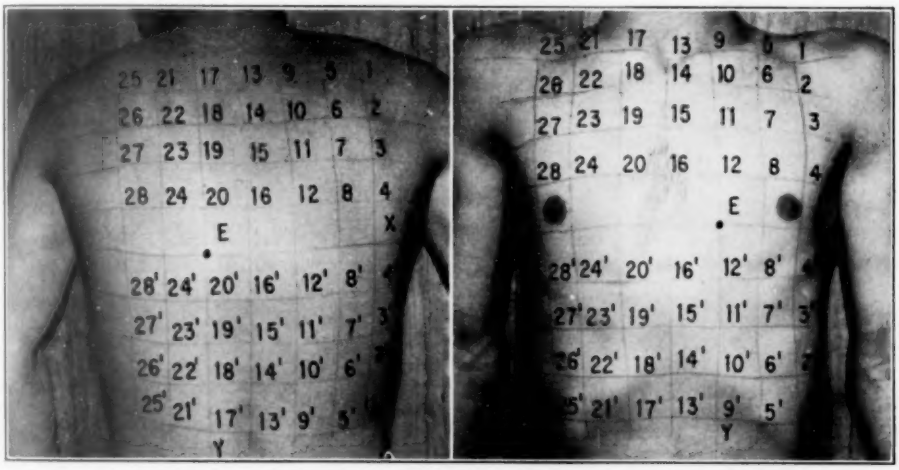


Fig. 4.—An illustration of the mapping of the human torso with symmetrical points above and below the Y_0 plane.

Results. All subjects demonstrated similar results for a portion of the surface points, although considerable variability was noted between individual subjects for some surface points. Over the back on the right side perfect cancellation by comparative vectorgrams was obtained (Fig. 5). Good cancellation was obtained over the left back but could not be considered as perfect as over the right back. Greater variability also existed over the left posterior thorax. Good acceptable cancellations were obtained in most subjects from surface points 12 cm. or more above and below the Y_0 plane over the anterior thorax. The anterior thorax presented the greatest variability between individual subjects. Many of the comparative vectorgrams less than 12 cm. from the Y_0 plane demonstrated lack of similarity to the reference vertical lead over the back and, therefore, did not represent a true vertical (Y) lead. These vectorgrams appeared as loops rather than as a straight line.

The calculated dR factor demonstrated a fairly consistent trend although considerable individual variation was noted (Fig. 6). In general the closer the surface point to the E point the smaller the dR factor. Not infrequently the points 12 cm. to the right of E point over the back (p5, 6,

7, 8) had comparable or a slightly greater dR factor than points 16 cm. to the right of E point (p1, 2, 3, 4). This is compatible with the individual variation in the normal rounding of the thorax on approaching the posterior axillary line. The dR factor diminished progressively on approaching the Y_0 plane. The dR factor was in general much smaller over the anterior thorax compared to similar locations over the back.

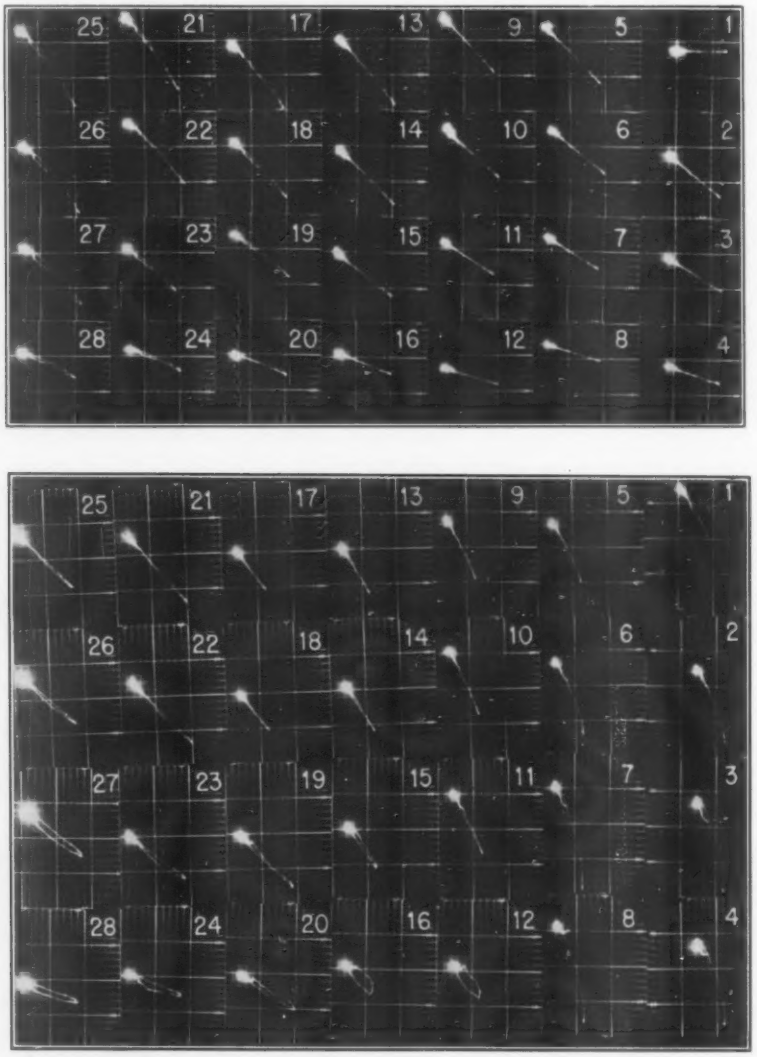


Fig. 5.—The cancellations by the comparative vectorgram techniques are demonstrated for the back (above) and anterior thorax (below). Note over the back the systematic decrease in vertical inclination of the vectorgram from 2 to 4, 5 to 8, etc. The amplification was reduced by ½ for all comparative vectorgrams recorded from the anterior thorax after the initial comparison of p1 — p1′ due to large amplitude.

Variations in the dR factor from one measurement to another were noted in the same subject. A marked variation was related to body position: with the reference lead attached and taped in place, its value was calculated for the subject lying prone (face down) and again while recumbent (lying on the back). The dR factor was most often decreased over 10% with the subject on his back as compared to lying face down. One subject showed a 22% decrease in the dR factor. The diminished dR factor demonstrates the influence of the heart moving backward toward the spine and closer to surface points p1 and p1′. Minor variations in the calculated dR factor were noted with the respiratory phase. These may be due to changes in the Y component of the dipole vector secondary to changes in excitation, or changes in cardiac position, or both.

Several subjects studied had a leftward electrical axis with a very small Y component. These subjects were more difficult to study than those with a vertical electrical axis. Since the Y component should theoretically be the only measurement obtained, perfect cancellation of X and Z components ($+X - X$, $+Z - Z$) leaves a very small measurement. In some nothing of consequence was recorded. Increased amplification magnified both the small Y component and the errors of unbalanced X or Z contributions.

Discussion. The results of comparative vectorgram analysis indicate that potential over much of the area over the anterior thorax of the human subject does not represent a simple dipole vector. This is hardly surprising, as some of the points are closer to the heart than the diameter of the left ventricle. The demonstration of failure of the dipole concept with proximal surface points and its validity at surface points roughly 15 cm. or more distant from E point is in good agreement with previous volume conductor experiments on the isolated mammalian heart (Hartmann *et al.*[7]). The departure from simple dipole representations is no small amount.

These results raise serious questions concerning the validity of the concept that measurements from any leads using the left precordium for electrode sites represent a dipole vector. Vectorcardiographic reference systems utilizing these locations are not representing a simple dipole effect. While the Frank reference system has enjoyed much popularity as a true electrically balanced orthogonal reference system, it uses the left precordium. Second thoughts concerning its validity and the wisdom of using it as a standard to evaluate less complicated VCG reference systems are warranted.

The determination of the dR factor, unlike torso model studies, permits evaluation of all the biological variables. The living human torso has sufficient technical complications, including lack of homogeneity and the influence of the reflectance boundary that a simple method of evaluating the influence of distance and resistance is extremely practical. Moreover, these studies demonstrate that body position alone may cause a 10% variation in the same subject. Artificial models do not reflect the normal expected biological variations. The influence of biological variations in the same subject as well as variations between different subjects makes it obvious that leads which are within 10% accurate in measuring their expected component are acceptable. The data from a perfectly designed phantom model experimental determination will be expected to vary this degree when applied to the human subject. Failure to recognize these biological variations leads to unnecessary refinements beyond the realm of practicality.

The variability of the dR factor

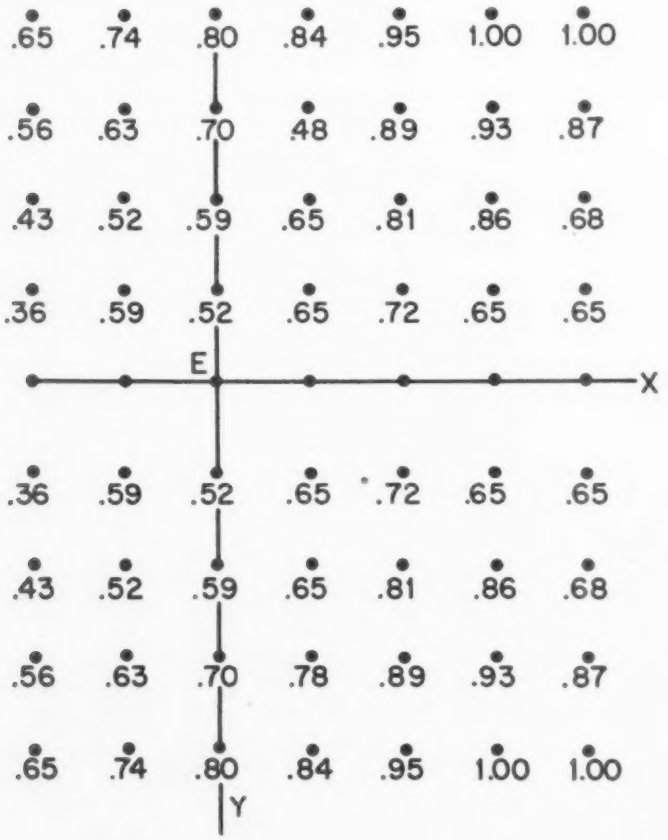
noted from subject to subject strongly suggests that small series of 1 or 2 subjects studied in detail falls far short of an adequate survey of the electrical problems indigenous to the human body.

The demonstration of complete cancellation by the comparative vectorgram at selected points over the back demonstrates that the E point was correctly located in its vertical position. Cancellation would not have occurred repeatedly unless the center was correctly located and unless the dR factor at comparable points above and below the Y_0 plane were reasonably equal.

The determination of the relative dR factor for multiple surface points provides the basis for locating lead sites for electrically balanced leads. It also provides a means of calculating the relative sensitivity of a bipolar lead. The relative contribution of the X, Y, Z vector components to a surface point can also be determined. This information is inherent in the basic formula of relative sensitivity for a given balanced lead.

$$\text{Lead Sensitivity} = \frac{\text{Coordinate Lead Length}}{\text{dR}}$$

This information will be utilized in another report to develop an electrically balanced vectorcardiographic reference system and lead analysis based on the determinations of the dR factor.



By using the dR factor other leads used in electrocardiography and vectorcardiography can be evaluated. Since the method is simple it is easy to determine the effects of various lead systems in the individual subject.

Summary. 1. A simple method is developed to determine the influence of distance and resistance between the heart and surface points over the body.

2. The electrical activity of the heart can be represented as a dipole when measured from body surface points sufficiently remote from the heart. In the average adult male this distance is approximately 15 to 20 cm. from the center of the left ventricle.

3. The human body has predictable variations in resistance between the heart and surface points. The resistance above Y_0 plane is comparable to the resistance at a similar point below the Y_0 plane, over the back anterior and extreme upper or lower thorax.

4. The relative effect of resistance and distance between the heart and various points over the body surface can be calculated for any individual subject.

5. The region over the anterior thorax

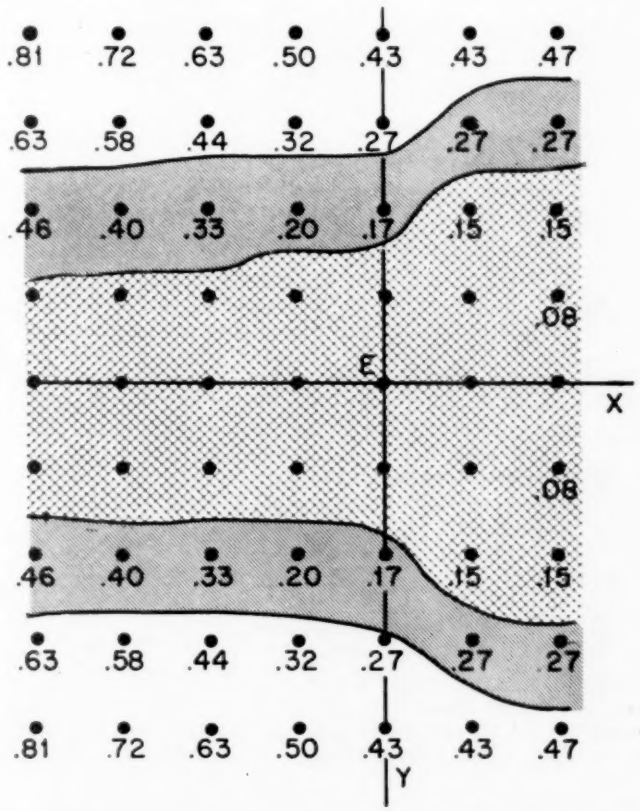


Fig. 6.—The calculated dR factors expressed in decimal relation to p1 and p1′ over the back are mapped out over the back and anterior thorax. The center area over the anterior thorax is the area of failure of cancellation. The gray area corresponds to fair cancellation. The white area corresponds to the regions sufficiently remote from E point to demonstrate good cancellations.

close to the heart does not behave like more remote sites due to the failure of simple representation of the dipole concept or other complicated factors pertaining to the live human torso's behavior as a volume conductor.

APPENDIX. The simple formula for calculation of relative dR values is derived as follows:

$$Vp1y = -VE_y \times LY/dR$$

and

$$Vp1'y = +VE_y \times LY/dR$$

The negative VE_y symbolizes a vector directed away from p1 and the positive VE_y symbolizes a vector directed toward p1'.
It was noted in the manuscript that electrically balanced bipolar leads of Y coordinate nature resulted in the cancellation of the Vpx and Vpz values thus

$$Vp1'y - Vp1y = Vp1' - Vp1$$

One may substitute,

$$Vp1' - Vp1 = (VE_y \times LY/dR) - (-VE_y \times LY/dR) \text{ or}$$
$$Vp1' - Vp1 = 2\ VE_y \times 2LY/dR.$$

Since 2LY is equivalent to the geometric length between p1 and p1' one may write the equation

$$Vp1' - Vp1 = 2VE_y \times \frac{Lp1 - p1'}{dR}$$

To solve for dR the equation may be expressed,

$$dR = \frac{2VE_y \times Lp1 - p1'}{Vp1' - Vp1}$$

In an exactly similar fashion the dR factor for p2 or p2' may be expressed,

$$dR = \frac{2VE_y \times Lp2 - p2'}{Vp2' - Vp2}$$

If one wishes to express any other dR factor relative to the dR factor for a reference lead such as p1 and p1', this may be expressed as a decimal fraction

$$dR_2/dR_1$$

By substitution the equation becomes

$$\frac{2\ VE_y \times Lp2 - p2'}{Vp2' - Vp2} \div \frac{2\ VE_y \times Lp1 - p1'}{Vp1' - Vp1} = dR_2/dR_1$$

or by cancellation

$$\frac{Lp2 - p2'}{Vp2' - Vp2} \times \frac{Vp1' - Vp1}{Lp1 - p1'} = dR_2/dR_1$$

If the dR factor for p1 is 1.00 the dR factor for p2 is expressed as a decimal fraction either smaller or greater than the dR factor for p1, if greater the influence of distance and resistance is greater between VE and p2 and results in a smaller Vp at p2, if smaller than 1.00, less attenuation due to distance and resistance exists between VE and p2 resulting in a larger Vp at p2.

REFERENCES

1. **Burger, H. C., and Van Milaan, J. B.:** Brit. Heart J., **8**, 157, 1946.
2. **Iidem:** Ibid., **9**, 154, 1947.
3. **Iidem:** Ibid., **10**, 229, 1948.

4. **Duchosal, P. W.,** and **Sulzer, R.:** La Vectorcardiographie. Basel: S. Karger, 1949.
5. **Frank, E.:** Am. Heart J., **47,** 757, 1954.
6. **Frank, E.,** and **Kay, C. F.:** Ibid., **46,** 195, 1953.
7. **Hartmann, I., Veyrat, R., Wyss, O. A. M.,** and **Duchosal, P. W.:** Cardiologia, **27,** 129, 1955.
8. **Nelson, C. V.:** Circulation Res., **3,** 236, 1955.
9. **Smith, G. B.,** and **Lamb, L. E.:** Am. J. Med. Sci., **237,** 434, 1959.

SUMMARIO IN INTERLINGUA

Un Studio Del Torso Human Como Conductor De Volumine, Per Medio De Un Analyse Comparative De Vectogrammas: Le Factor dR

1. Es disveloppate un simple methodo pro determinar le influentia de distantia e resistentia inter le corde e punctos al superficie del corpore.

2. Le activitate electric del corde pote esser representate como un dipolo si illo es mesurate ab punctos al superficie del corpore que es sufficientemente distante ab le corde. In typic masculos adulte, iste distantia es approximativemente 15 a 20 cm ab le centro del ventriculo sinistre.

3. Le corpore human ha predicibile variationes in le resistentia inter le corde e punctos superficial. Le resistentia supra le plano Y_0 es comparabile al resistentia a un simile puncto infra le plano Y_0, super le dorso e le thorace supero- o infero-anterior extreme.

4. Le effecto relative de resistentia e de distantia inter le corde e varie punctos al superficie del corpore pote esser calculate pro omne subjecto individual.

5. Le region super le thorace anterior proxime al corde non se comporta como plus distante sitos. Isto es causate per le facto que alora le notion del dipolo non es representate simplemente o per altere complexe factores que ha a facer con le comportamento del vive torso human como conductor de volumine.

EOSINOPHILIC PNEUMONOPATHY (LOEFFLER'S SYNDROME) CASE REPORT DESCRIBING TWO ATTACKS IN THE SAME PATIENT AND CONTRASTING STEROID WITH NONSTEROID THERAPY

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AND

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This report describes a case of acute eosinophilic pneumonopathy (Loeffler's Syndrome) in a 23-year-old white male army veteran who responded readily to hydrocortisone. There was dramatic clinical improvement, a fall in temperature to normal level within 36 hours, and almost complete clearing of pulmonary infiltrations in 10 days. Several cases showing similar favorable response to either ACTH or cortisone have been reported (Herbert, DeVries and Rose[1], Mark[2], Reeder and Goodrich[3], Sanjivi, Thiruvengadam and Friedmann[4,5], Vines and Clark[6]). The reason for reporting this case is that an opportunity was afforded to compare the clinical course of this cortisone-treated attack with a virtually similar attack experienced by the same veteran in 1955 while on duty with the army in Japan. The 1955 attack demonstrated the natural history of the disease when untreated with either ACTH or cortisone. Both attacks had similar onset and showed almost identical degree of involvement on initial roentgenographic examination of the chest at the time of admission to the respective hospitals.

For the 1955 attack, the veteran was hospitalized for 6 months, and was kept on bed rest. His fever lasted for 40 days, it required about 60 days for the lungs to clear, and there was slow clinical improvement (Fig. 1). In addition, the attack was complicated by right pleural and pericardial effusions.

In contrast, with hydrocortisone, the 1958 attack required 20 days of hospitalization, the fever lasted for 36 hours, there were no complications, the clinical improvement was rapid, and the chest roentgenograms showed practically complete clearing in about 10 days (Fig. 2).

Both attacks began with upper respiratory infections which followed moderate exhaustion and exposure to inclement weather. The infections spread to the bronchi and lung parenchyma and were accompanied by severe cough productive of sputum which was blood-tinged at times, marked dyspnea, sweats, anorexia, fever, and weakness. The veteran gave no history of allergy, past or present, and there was no familial history of allergy.

Case Report. THE 1958 ADMISSION TO THE OTEEN VETERANS HOSPITAL. The veteran was admitted on October 26, 1958, complaining of shortness of breath, weakness, cough, rusty sputum, anorexia, sweats, and loss of weight. For several days following October 1, 1958, he was exposed to rainy weather and kept getting wet going from one building to another on the college campus where he was a student. He wore neither head cover nor raincoat. He contracted a head cold and a progressively severe cough. His dyspnea increased, he lost his appetite, had night sweats,

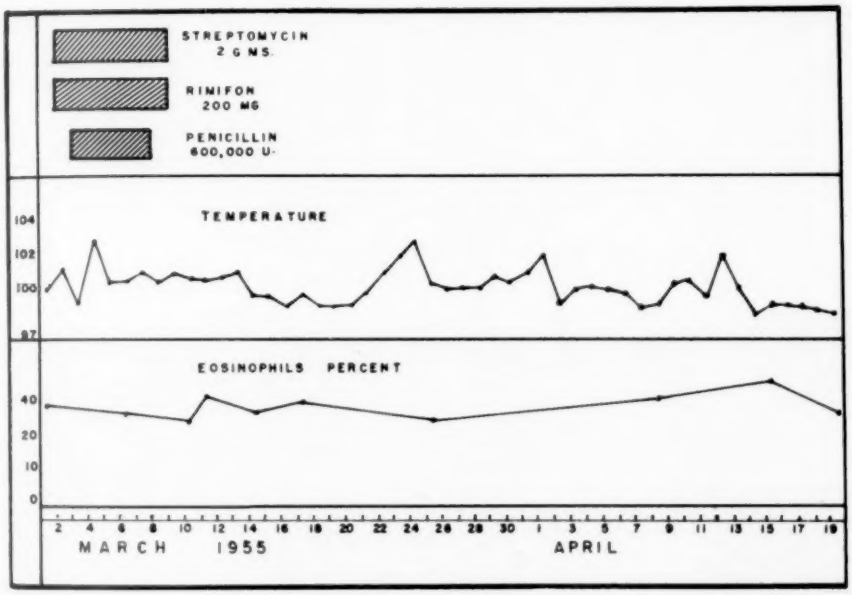

Fig. 1.—Data on course in hospital in 1955.

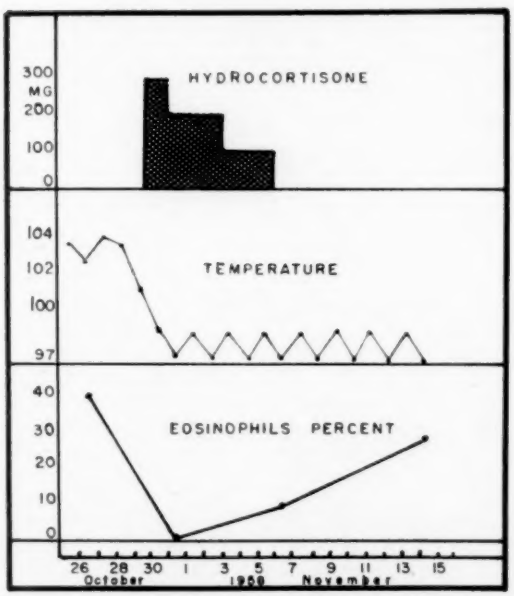

Fig. 2.—Data on course in hospital in 1958.

became weak, and lost 10 pounds. He continued to attend classes until October 24. On October 25 he consulted a private physician who, because of the extensive roentgenographic findings, recommended immediate hospitalization as a tuberculosis suspect. The veteran entered Oteen on October 26. On admission he was acutely ill, coughed often, and had a rusty sputum. He was prostrated and anorectic. His temperature at 4 p.m. was 99.8° F. and at 7 p.m. it was 103.6° F. Physical examination revealed large areas of both lungs with bronchial breathing. There were no moist rales and no wheezes. The heart rate was regular, rapid, and the blood pressure was 130/70 mm. Hg. The respirations were increased. The rest of the examination was normal.

The urinalysis showed a trace of albumin. The sputum was negative for acid-fast bacilli on smear of concentrate and showed Gram-positive cocci in short chains and pairs. Sputum cultures yielded *Neisseria catarrhalis*, alpha streptococcus, and pneumococcus. Skin tests with blastomycin, coccidioidin, and histoplasmin were negative. The tuberculin test was positive. The white blood cell count was 13,000 with 51% neutrophils, 7% lymphocytes, 2% monocytes, and 40% eosinophils. The red blood cell count was 4.2 million, hemoglobin 11.3 gm., sedimentation rate 53 mm. in one hour, and the hematocrit value 36. A chest roentgenogram on October 27 revealed a normal cardiac silhouette, large areas of pneumonic consolidation in both lungs with scattered soft "woolly" areas of infiltration (Fig. 3).

On October 27, because of toxicity and fever, he was given 600,000 units of penicillin at 9 a.m. and at 8 p.m. Similar injections were given on October 28 and 29 without effect. Because of the possibility that the lesion might be tuberculous he was given INH, 100 mg. t.i.d., and streptomycin, 1 gm. intramuscularly, on October 29. Similar doses were given on October 30 and 31, when they were discontinued.

When the eosinophilia of 40% was noted, eosinophilic pneumonopathy was suspected. A stained sputum preparation showed 42% eosinophils. Hydrocortisone sodium succinate was given on October 30 as follows: 100 mg. intramuscularly every 4 hours for 3 doses, followed by 100 mg. intramuscularly every 12 hours for 3 days, and 50 mg. intramuscularly every 12 hours for 3 days. Within 6 hours there was considerable subjective improvement manifest by alertness, some improvement in appetite, and an increase in strength. The temperature fell to normal with-

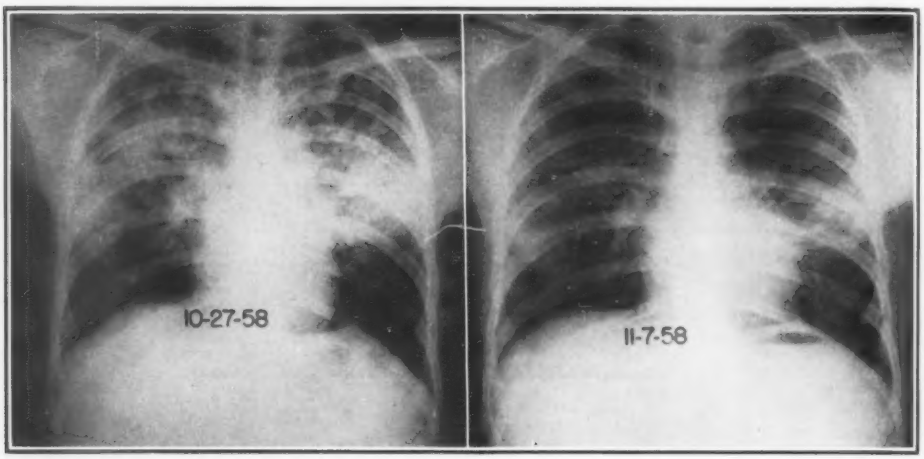

Fig. 3 Fig. 4

Fig. 3.—Extensive bilateral infiltrations; roentgenogram made 3 days prior to start of hydrocortisone therapy.

Fig. 4.—Shows marked clearing 7 days after start of therapy and 2 days after completion of therapy.

in 36 hours and remained normal thereafter. On November 1, auscultation revealed areas of bronchial breathing to be still present. On November 3, these areas were smaller, but no moist rales, which usually accompany resolution of a pneumonic process, were heard. On October 31, the white blood cell count was 11,700 and no eosinophils were seen. The red blood cell count was 4.8 million and the hemoglobin 13.4 gm. Clinical improvement was sustained. Roentgenograms on November 4, 7, and 12 showed progressive clearing (Figs. 4, 5). His appetite returned and he regained 7 pounds. He felt well and regained his normal strength. Because he was anxious to return to college and avoid losing an entire semester he was discharged on November 15, 1958, after 20 days of hospitalization. A follow-up examination on November 26 showed no physical abnormality and a roentgenogram showed both lungs to be clear (Fig. 6). A follow-up examination on December 22 found the veteran to be symptom free. However, a roentgenogram showed some nodular infiltrations in both upper lung fields (Fig. 7). A white blood cell count was 6,200 with 20% eosinophils. The most recent follow-up roentgenogram on February 14, 1959, showed both lungs to be clear. The cardiac silhouette was normal.

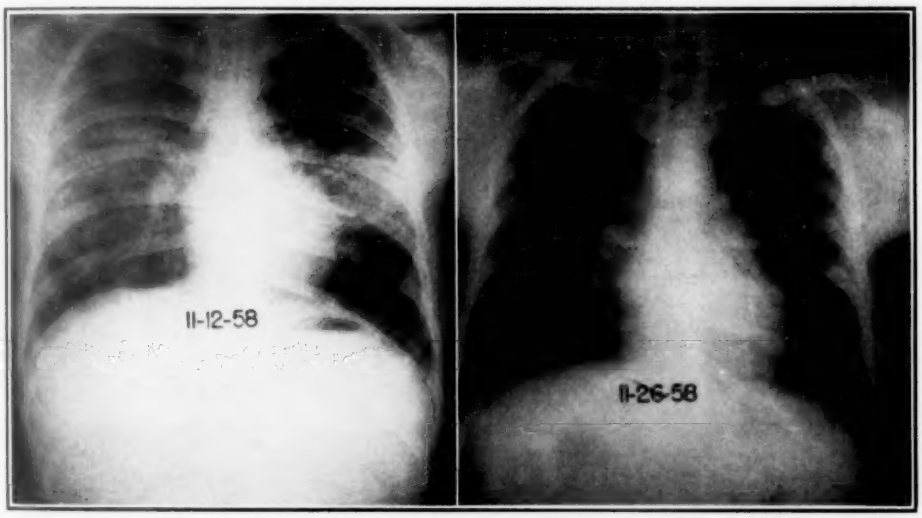

Fig. 5 Fig. 6

Fig. 5.—Status at time of discharge; slight residual infiltration is present bilaterally.

Fig. 6.—Shows normal lung fields 21 days after completion of therapy.

THE 1955 ADMISSIONS TO ARMY HOSPITALS IN JAPAN. In February, 1955, the veteran was a 19-year-old clerk-typist with an Army Graves Registration Team in Japan. Following an all day exposure to inclement weather he contracted a cold and was treated at a dispensary in Camp Kokura from February 15 to March 1. He received two injections of penicillin and was given cough mixtures. His cough became worse and was productive of blood-tinged sputum at times. He became anorectic and short of breath. Finally he could not walk even short distances without becoming severely dyspneic. He developed substernal soreness and pain. On February 2, a white blood cell count showed 16,000 cells with 69% neutrophils, 3% lymphocytes, 27% eosinophils, and 1% basophils. The red blood cell count was 2.5 million, hemoglobin 10.5 gm., and the hematocrit value 34. He was admitted to the 8162nd Hospital on March 2 for "medical observation for fever, pulmonary infiltration, eosinophilia, and anemia."

Physical examination on admission revealed a thin, wasted, acutely ill white man who was short of breath even while talking. The cheeks were flushed. The pulse was 120 and the blood pressure 80/55 mm. Hg. On auscultation, both lungs showed several areas of bronchial breathing. No moist rales or

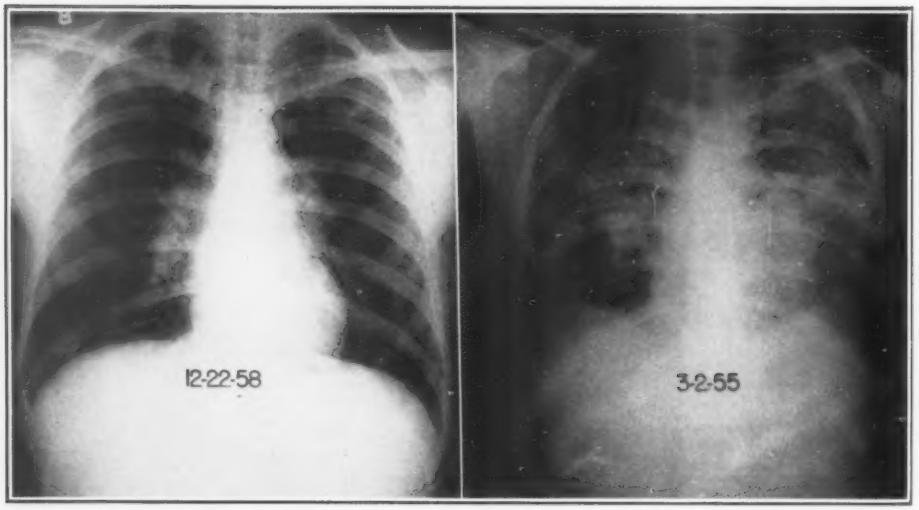

Fig. 7 Fig. 8

Fig. 7.—Outpatient roentgenogram made 47 days after completion of therapy; shows small nodular infiltrations in both upper lung fields.

Fig. 8.—Extensive bilateral infiltrations at the time of admission to hospital in 1955.

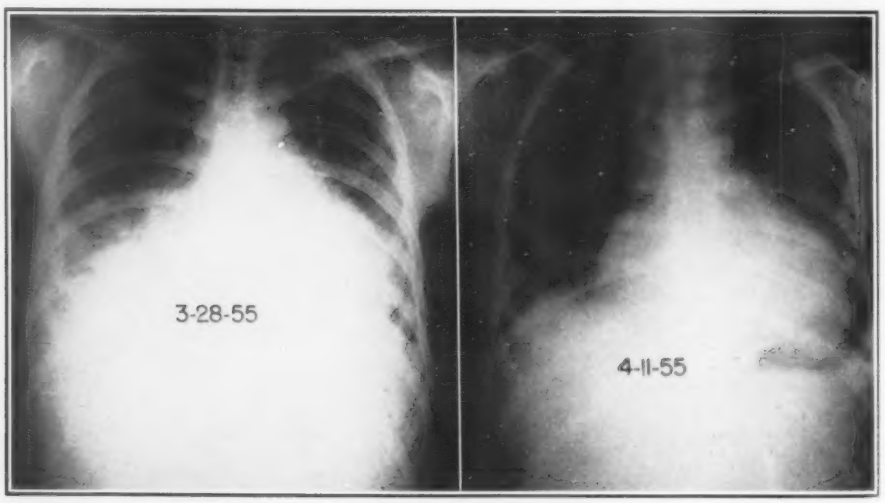

Fig. 9 Fig. 10

Fig. 9.—There has been some clearing. Note signs of pleural and pericardial effusions.

Fig. 10.—There has been further clearing. Signs of pericardial effusion are still present.

wheezes were heard. The rest of the examination was normal.

A chest roentgenogram on March 2 showed extensive bilateral "patchy" areas of dense infiltrations most marked in the central portions where the lesions were confluent (Fig. 8). However, no area of lung was entirely free of infiltrations. A chest roentgenogram on March 6 showed slight clearing in the right mid-lung and an increase in the left base. Roentgenograms on March 11 and 14 showed no change. His temperature ranged from 99° to 100° F. with pulse in proportion. On March 7, the white blood cell count was 18,900 with 63% neutrophils, 13% lymphocytes, and 34% eosinophils. The red blood cell count was 3.6 million, hemoglobin 11.4 gm. and the hematocrit value 37. The sputum showed *Neisseria catarrhalis* and hemolytic streptococcus on culture. The blood serology was negative.

He was given streptomycin, 1 gm. twice daily, and INH, 200 mg. daily, for one week because of a report that acid-fast bacilli were present on a smear of concentrated sputum. These drugs were discontinued when this report proved to be false. He was also given 600,000 units of penicillin daily for 5 days without effect. Several diagnoses were considered: tuberculosis, sarcoidosis, parasitic infestation, Loeffler's syndrome, and pneumoconiosis. Roentgenograms of the bones showed no abnormality. The patient was then transferred to the Army Tokyo General Hospital on March 16, 1955. He remained at this hospital until August 11, 1955, when he was discharged to limited duty. During this hospitalization he was on bed rest, was febrile until April 15, improved slowly and gradually regained his appetite and strength.

He had many laboratory tests and diagnostic procedures. The following special tests showed no abnormality: serum chloride, calcium, alkaline phosphatase, total proteins, cholesterol, and cholesterol esters. No malarial parasites were seen on blood preparations. The skin tests with histoplasmin and coccidioidin were negative. The tuberculin test was positive. Sputum cultures were negative for fungi and acid fast bacilli. Liver function tests were normal and a liver biopsy showed no abnormality on histological examination. A stool examination on March 14 showed hookworm ova. However, subsequent stool examinations were negative for ova. Between March 15 and April 22, numerous blood examinations revealed a moderate leukocytosis, ranging from 11,000 to 13,000. After April 22 the white blood cell counts were within normal limits. The eosinophils, how-

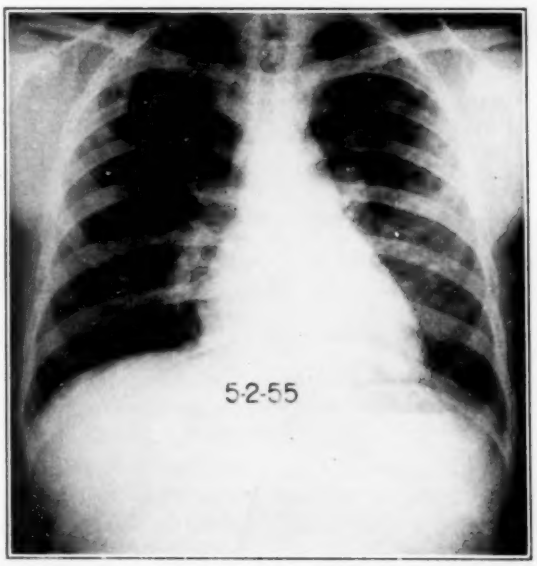

Fig. 11.—There has been complete clearing.

ever, were always elevated. They ranged from 28 to 52% up until May 6. After May 6, the percentage gradually fell to a low of 9% at the time of discharge.

Roentgenographic examinations of the upper gastrointestinal, biliary, and genitourinary tracts showed no abnormality. On March 28, a chest roentgenogram, in addition to scattered infiltrations in both lungs, showed evidence of a right pleural effusion. There was also an increase in the transverse diameter of the heart shadow (Fig. 9). During fluoroscopic examination of the esophagus and stomach on March 19 there was evidence of diminished cardiac excursions which was attributed to a pericardial effusion. On April 15, a pericardial aspiration yielded 7 ml. of serosanguinous fluid which was negative on culture for pyogenic and acid-fast bacilli. The electrocardiograms, which were normal up until March 17, showed changes compatible with a pericardial effusion. A tracing made on March 17, showed an atrio-ventricular rate of 104; PR interval .14; QRS interval .08; QT interval .27. The RS–T segment showed depressed V3, 4, 5, 6. T waves were inverted in Leads II, III, avF, V3, 4, 5, 6. These changes were interpreted as being compatible with the pericarditis: The tracing on April 25 and subsequent tracings were normal coincident with the disappearance of the pericardial effusion.

During May, June, and July, his course was one of gradual improvement. He was discharged from the hospital on August 2, 1955, with recommendations that he should "avoid exposure to severe climatic conditions, have no field duty, physical training or marches, and no strenuous exercises."

Discussion. The two attacks of eosinophilic pneumonopathy are so much alike in mode of onset and in the clinical, hematological, and roentgenographic aspects, that they are comparable in the evaluation of the therapeutic effect of hydrocortisone on the syndrome. The prompt effect of the hormone on the eosinophilia, fever, subjective symptoms, and pulmonary infiltrations, warrants the conclusion that the hormone had a powerful and beneficial effect on the fundamental etiologic factor. That the effect was temporarily suppressive is evident from the presence of small nodular lesions in both upper lung fields, without clinical symptoms, on the follow-up roentgenogram of December 22, 1958, which was taken 47 days after cessation of therapy. The persistence of the eosinophilia is also an indication that the fundamental factor is still operating. The fact that both attacks were apparently precipitated by physical exhaustion is significant. Exhaustion has been mentioned as a possible precipitating factor in a case report by Vines and Clark[6].

Summary. An army veteran had two attacks of eosinophilic pneumonopathy (Loeffler's syndrome): one in 1955 while on duty in Japan, the other in 1958 while attending college. An opportunity was afforded of comparing the 1958 attack, which was successfully treated with hydrocortisone, with the almost identical attack in 1955 which was not treated with steroid. The 1955 attack thus afforded the chance to observe the natural history of the disease in this patient. He gave no history of allergy, personal or familial, which could have caused the attacks. Both episodes followed moderate physical exhaustion and exposure to inclement weather which caused upper respiratory infections that soon led to involvement of the bronchi and pulmonary parenchyma.

REFERENCES

1. **Herbert, P., De Vries, J. A.,** and **Rose, B.:** J. Allergy, **21,** 12, 1950.
2. **Mark, L.:** Dis. Chest, **25,** 128, 1954.
3. **Reeder, W. H.,** and **Goodrich, B. E.:** Ann. Int. Med., **36,** 1217, 1952.
4. **Sanjivi, K. S., Thiruvengadam, K. V.,** and **Friedmann, H. C.:** Dis. Chest, **28,** 76, 1955.
5. Iidem: Ibid., **28,** 88, 1955.
6. **Vines, R. W.,** and **Clark, D.:** New England J. Med., **244,** 826, 1951.

(Interlingua on page 650)

PROGRESS
OF
MEDICAL SCIENCE

THERAPEUTICS

UNDER THE CHARGE OF

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TRANQUILIZING DRUGS

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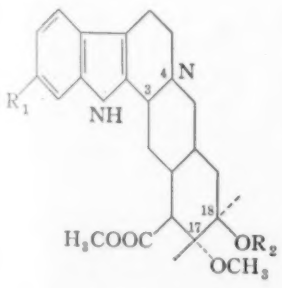
THE designation of a group of drugs as "tranquilizers" is based on the belief that their actions on behavior are distinct from the way in which other drugs modify transactions with environment of animals and man. Such a distinction is in the first place revealed at a clinical level; however, when reference is being made to mechanisms of action, it stands for complex patterns of changes describable, at least in principle, within physiological, biochemical and psychological terms and concepts. Although ultimately a mutual correspondence between these explanatory domains may be established, such a situation does



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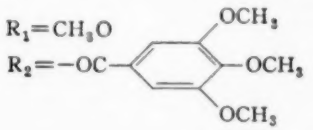

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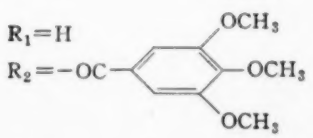

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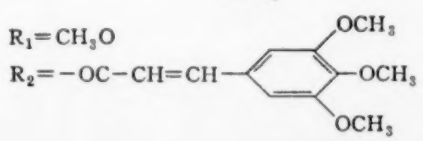
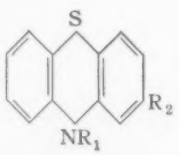


not exist at present except within very narrow limits. The following discussion will, therefore, be restricted to a description of some of the relevant findings grouped under different procedural categories.

STRUCTURE-ACTIVITY RELATIONSHIP. Amongst naturally occurring substances, alkaloids of *Rauwolfia serpentina* have attracted the attention of investigators since about 1930. Preparations of this plant, however, have been in use in the popular medicine of India for many centuries[11,34,119]. Tranquilizing activity is restricted to some of the alkaloids of the Rauwolfia genus which are classified as tertiary indole bases (review in[178]).

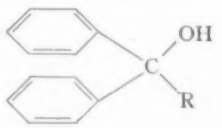
The trimethoxy benzoyl group at C_{18} is apparently essential for the tranquilizing activity since products obtained by hydrolysis of this ester bond are inactive. The methoxy group in position 1 is not required for this activity. Replacement of the H- atom at the indole nitrogen or quaternization of the nitrogen in position 4 leads to loss of reserpine-like activity. The importance of steric factors is illustrated by the fact that the 3- iso compounds are inactive[150].

A series of compounds derived from phenothiazine represent a group of pharmacologically active and pluripotent structures[168]:



Tranquilizing activity is apparently favored by the presence of a dimethylaminopropane side chain in position R_1 (Promazine: R_2=H) and halogenation in position R_2 (chlorpromazine: R_2=Cl; Vesprin: R_2=CF_3) or by an N-alkyl piperazine side chain in position R_1 (Compazine: R_2=Cl; Trilafon: R_2=Cl; Dartal: R_2=Cl); N-alkyl piperidyl derivatives of phenothiazine (R_2=H) are also active (for example, Mepazine).

Tranquilizing activity is also possessed by some diphenyl methane derivatives in which case substitution of R by piperidyl (for example, azacyclonol) accounts for a high degree of specificity with respect to the central action. However, substitution of R by diethylamino acetic acid also leads to a compound of interesting, though less specific, action on behavior (that is, Benactyzine).



Reference will also be made in this review to substituted propanediol derivatives such as Meprobamate.

DRUG-INDUCED BEHAVIOR CHANGES IN ANIMALS. a) *Chlorpromazine.* In the course of a comprehensive pharmacological study, it was noted that chlorpromazine (Chl.) interfered with the performance of rats which had previously been trained to climb a rope in response to an auditory stimulus[43]. In this respect, Chl. resembled a large number of antihistaminic drugs[177]. The performance of rats, trained to secure a food reward after the sounding of a buzzer, was determined after administration of Chl.: the decrease of successful responses was proportional to the logarithm of the dose within a range of 3.0 to 9.0 mg. per kg.[78]. Conditioned responses in rats were also studied by Cook *et al.* [41] with similar results. In the same experiments, pentobarbital reduced the percentage of successful performance only in doses which produced marked ataxia. Morphine, on the

other hand, caused a specific and significant reduction of successful responses. Chlorpromazine (1.25 mg. per kg.) suppressed the avoidance response for several hours in rats that had been trained to hurdle a barrier to avoid an electrical shock[115]. Also in these experiments, a progressive loss of avoidance behavior correlated linearly with the logarithm of the dose. During repeated drug administration for several days, an extinction of the avoidance response was accomplished which persisted through the post-treatment period. It was suggested that this prolonged effect represented an actual relearning of the avoidance situation by animals whose fear motivation was suppressed by the drug[116].

A conditioned fear response was studied more directly by Hunt[59] using the technique of Estes and Skinner[58]: essentially, this involves the superposition of a conditioned emotional disturbance upon a previously established lever pressing habit. Chlorpromazine at a low dose level (1 to 2 mg. per kg.) interfered with the learned behavior of lever pressing and diminished the manifestations considered characteristic for the conditioned emotional response (CER), that is, defecation and "freezing" of the animal. Complete block of fear expression was obtained with high doses (10 mg. per kg.); these doses rendered the animals ataxic. It appears highly significant that methantheline bromide (Banthine), a peripherally acting cholinolytic, also lowered incidence and modified the qualitative aspects of the CER, although it does not cross the blood brain barrier. It must be remembered that Chl. in high doses also exerts significant peripheral autonomic blocking activity[43].

Temporary loss of conditioned avoidance reaction after Chl. was observed in monkeys by Smith *et al.*[156], and the effect was qualitatively and quantitatively the same in animals with intact brain or after extensive bilateral removal of the frontal or temporal lobe, or both lobes. Conditioned reflexes in cats were much more sensitive to depression by Chl. if the conditioned stimuli were presented to the periphery than to the cerebral cortex directly[139]. This differential effect of Chl. points to some action on the afferent system.

A different approach to the analysis of behavior effects of tranquilizers was suggested by Olds[121]. The method is based on the observation that rats under suitable experimental conditions apply electrical stimuli to themselves through permanently implanted electrodes with a frequency of 500 to 2000 shocks per hour, if the electrode tips are located in hypothalamic or palaeocortical areas[122]. The frequency of self-stimulation was significantly reduced by Chl. (2.5 mg. per kg.), whereas barbiturates did not exert any effect unless administered in hypnotic doses. The inhibitory action of Chl. on self-stimulation was more marked when the stimuli were applied to the posterior than to the anterior hypothalamus[123]. This effect of Chl. was still more marked in monkeys (Cebus) in which the frequency of self-stimulation was increased above normal during the withdrawal period after addiction to morphine[173].

Effects of Chl. can also be noted more simply by direct observation of animal behavior without the aid of special techniques: a taming action of Chl. on aggressive Rhesus monkeys was reported[44]. The monkeys showed a tendency to assume bizarre postures which could be maintained for prolonged periods of time. Tremulousness of movements and convulsions appeared at higher dose levels[57]. The activity of cats was decreased by Chl.

and this effect was accompanied by a lowering of their sociability score[120]. The innate behavior pattern of male Siamese fighting fish *(Betta splendens)*, consisting in an intimidation display, was suppressed[179]. Chl. depressed sexual behavior in the male rat[181].

Artificially provoked rage reactions, like the "sham-rage" of decorticate cats[45] and the morphine-produced mania of cats[107], are significantly depressed by Chl. in relatively low doses.

b) *Rauwolfia alkaloids.* Reserpine was found to have a taming effect on Rhesus monkeys resulting in a behavior which was characterized as "insulation from environment"[151]. A diminution of "sociability" was noted in cats, other categories of behavior remaining essentially unaltered[120]. The morphine-induced mania of cats was enhanced[107]. The effects of reserpine were thus in some instances distinctly different from the Chl. induced behavior changes. Such a distinction also existed with regard to the nest-building activity of rats, reserpine having a persistent depressant effect[153].

Rats trained to run for food reward[78] or to avoid shock by jumping across a barrier upon presentation of an auditory stimulus[87] were not affected by reserpine in doses of 1.5 mg. per kg. and 1 to 2 mg. per kg. respectively. In high doses (that is, 25 mg. per kg., twice administered orally, 17 hours apart), reserpine reduced avoidance responses by 65% without altering escape behavior[42]. Reserpine did not in rats prevent the acquisition of a CER, even when the drug was administered for 7 days (9.5 mg. per kg.) after which time the lever pressing rate for a water reward was considerably reduced[161]. There was also no significant difference in the resistance to experimental extinction of CER between control and reserpine-treated groups. A previously established CER (consisting of crouching, defecation, immobility and suppression of lever pressing) was, however, markedly reduced by reserpine (0.2 mg. per kg. daily for 4 days)[27]. Concomitantly with the diminution of the previously trained CER, a return to normal of the blood level of 17-hydroxy corticosteroids, increased during the development of CER, was noted in monkeys[113].

Differential effects of reserpine on conditioned responses were described for cats, depending on the nature of the cue: Reserpine affected the conditioned avoidance response to a visual cue much more severely than the same response to an auditory cue, this difference possibly being related to the relatively greater difficulty of learning the response to a visual cue, as evidenced by the greater number of trials necessary to establish the conditioned response in the visual as compared with the auditory learning situation; a visually mediated approach response (food reward) was considerably less affected by reserpine than behavior motivated by punishment[93]. These effects were produced by astonishingly low doses of reserpine (7.5 to 65 μg. per kg., intramuscularly; or 25 to 300 μg. total dose, into the lateral ventricle).

Differential interactions of reserpine with performance of rats as a function of specific behavior controlling variables (such as reinforcement schedule) were also noted by Sidman[148]: among the contingencies that generate behavioral processes, temporal discrimination was more severely interfered with than auditory discrimination. Reserpine suppressed in higher doses (1 mg. per kg.) all lever pressing behavior regardless of the type of reinforcement used. However, it was possible to restore lever pressing behavior transiently with amphetamine. The interference of reserpine with avoidance responses was found to depend on the shock schedule used; thus, a decline of avoidance responses was seen on a

20% shock schedule (that is, for every 5 times the animal waited a given interval without pressing the lever, a shock was given), whereas the rate of responding remained normal on a 100% shock schedule at the same dose level of reserpine[148]. No differential effect of reserpine (0.25 to 2.0 mg. per kg. per day) was, however, found on fear-and-hunger motivated escape behavior in rats[15].

Avoidance behavior of monkeys was tested by Weiskrantz and Wilson[172] utilizing an apparatus in which the animals could avoid shock by pushing a panel at least once every 10 sec.; impairment of the previously established avoidance behavior started about 2 to 3 hours after intramuscular injection of 0.75 mg. per kg. reserpine, and the avoidance response was eventually blocked in all animals. The effect of reserpine on this response was unaltered after amygdalectomy.

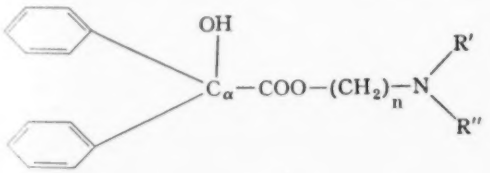
Loss of avoidance habit due to the action of reserpine was also noted by Smith *et al.*[155]. Extensive cortical ablation reduced the effectiveness of the alkaloid. Desmethoxy reserpine and rescinnamine acted in normal animals identically with respect to the depression of the avoidance habit, though their curve of action was somewhat different. Desmethoxy reserpine was significantly less active in animals with lesions of the frontal cortex, whereas rescinnamine was equally potent in normal and cortically damaged monkeys[156].

The effect of reserpine on the pecking behavior of pigeons revealed interesting aspects of the drug action[48]. Pecking was virtually abolished for 18 hours after single doses of 100 mg. Long lasting pauses of pecking activity occurred during the recovery phase at any time between the reinforcing stimuli if the performance was tested on a fixed ratio schedule: the animals appeared to be liberated from the normally powerful stimulus control of the performance schedule.

Reserpine depressed the rate of self-stimulation in rats through permanently implanted electrodes in hypothalamic and paleocortical areas[122], but the effect appeared only at high stimulation intensities, possibly as a consequence of petit mal states[123]..

c) *Diphenylmethane derivatives.* Azacyclonol altered the behavior pattern of normal cats in a similar way as Rauwolfia alkaloids by significantly decreasing the sociability score of the animals[120]. Conditioned avoidance behavior in monkeys was not affected by Azacyclonol in doses up to 20 mg. per kg.[156]. Motor activity of mice and rats was diminished when moderate doses were given, but excitation was caused by higher doses; dogs responded to Azacyclonol only with excitation. Morphine-induced stimulation of cats was suppressed and hexobarbital-sleeping time was considerably prolonged by Azacyclonol[30].

A series of benzilic esters was tested in rats under conditions of stress induced behavior[87]. While expecting conditioned or unconditioned electric shocks, the animals remained immobilized and tense; their attitude became normal after administration of benzilic acid esters of the following constitution:



For n = 2: R' and R'' methyl, ethyl or isopropyl
For n = 3: R' and R'' ethyl

Replacement of the hydroxy group at the α Carbon by Cl enhanced the effect. Another active compound in this test was scopolamine, but atropine, morphine and reserpine had only slight activity.

d) *Meprobamate.* Like chlorpromazine, meprobamate (100 mg. per kg.) reduced hostility in cats[120] and caused sedation in monkeys[13]. No significant effect on the acquisition, the extinction, or the manifestation of the CER could be noted in rats and there was no consistent interference with lever pressing for an aperiodic water reward (80 to 240 mg. per kg.)[90]. Conditioned reflexes were not specifically depressed in rats and monkeys[127]. Meprobamate was, however, effective in controlling savageness and irritability produced by lesions in the septal forebrain in rats. For about 2 weeks after placing the lesions, such animals exhibited a significantly reduced threshold for attack and an exaggerated startle response followed by violent running in the cage[26]. Meprobamate interfered in isolated mallard ducklings with the extremely rapid process of learning known as "imprinting," if they were presented with a decoy model of a male mallard duck at the critical age period from 13 to 16 hours after hatching; chlorpromazine did not alter imprinting as such, but prolonged the period during which imprinting was possible[82].

An evaluation of drug induced behavior changes in animals in more general terms is made difficult by the large number of variables, such as dosage schedule or behavior controlling, factors, used in any one particular test. It emerges, however, from the existing data that spontaneous and innate behavior patterns as well as classical and operant conditioning are accessible to quantitative modification (that is, alterations in degrees rather than in kind) by drugs. In the case of stress-induced somatic and autonomic manifestations, generally looked upon as analogous to "emotional reactions" on the human scale (CER), it appears that acquisition, established symptomatology and extinction can be modified differentially, depending on drug, dose schedule and experimental situation. Peripheral autonomic blockade may also play some role in disrupting such behavior patterns (for example, Chlorpromazine in high doses).

NEUROPHARMACOLOGIC ASPECTS. The relevant literature was exhaustively reviewed by Wikler[175]; the following discussion will, therefore, be restricted to a brief outline of what appears to be crucial evidence on effects of tranquilizing drugs which can be observed with current neurophysiological methods. The implicit assumption is generally made that a given drug effect will ultimately be found to originate from interference with the function of a particular morphological structure of the nervous system. However, this concept may prove to be too narrow to account for the actual effects. A description of activity, both normal and drug influenced, in terms of patterns of impulse distributions in time and space over the whole central nervous system might provide a more realistic representation of the events[77].

a) *Chlorpromazine.* The appearance of slow waves in the electroencephalogram, usually described as "synchronization," was observed by several groups of investigators in different animal species and in man (literature reviewed in[175]). To what extent this effect may be a consequence of depression of the ascending reticular formation (arousal system) is controversial. It is, however, certain that Chl. is much less active in depressing the EEG arousal response in cats following electrical stimulation of different levels of the activating system than are barbitu-

rates[96]. The issue is also complicated by differences between animal species since the EEG arousal response was markedly depressed in rabbits, particularly when pain was used as alerting stimulus[83,108]. But it was possible to show with preparations transected at C 1 ("encephale isolé") that Chl. abolished the awakening effects of adrenaline[21] and amphetamine[25] on the electrocortiogram. Electrical responses in the reticular formation evoked by stimulation of peripheral nerve or by intrareticular stimulation were enhanced by Chl. Furthermore, Chl. augmented the inhibitory control of the reticular formation on responses in the auditory pathway: Killam and Killam[97a] thus concluded that Chl. disturbed attention and consciousness by facilitating reticular input and conduction, and by making more effective a filtering interaction of the reticular formation with lateral sensory pathways. Recruiting responses (8 to 12 per sec. spindles) obtained by stimulation of the diffuse thalamic projection system in cats were enhanced by Chl. in low doses and depressed by doses above 5 mg. per kg.[97]; the threshold for behavioral arousal from the diffuse thalamic projection system was markedly raised by Chl.[97a]. Waxing and waning spindle burst activity was regularly elicited by Chl. (0.5 to 1.0 mg. per kg.) in cortical and subcortical areas, after transection of the spinal cord at a cervical or upper thoracic level, that is, presumably under conditions of diminished afferent drive of the brain stem[174]. Chl. failed to alter the recovery cycle of neurons of the thalamic relay as measured at the capsule[97] where barbiturates in a suitable dose range exerted a marked depressing action[95]. Preston[130] observed an increase of spontaneous electrical activity in the amygdaloid nuclear complex in cats after administration of Chl. in relatively large doses.

Chl. inhibited motor activity induced by cortical stimulation and suppressed postural responses elicited by stimulation of cerebellar cortex, cerebellar nuclei and reticular formation[46]. Mono- and polysynaptic reflex activity in spinal animals was not significantly interfered with[46,130]. It has since been shown that Chl. acts upon motor activity mainly by abolishing the supraspinal control of the gamma motor neurons with the result that the tonic efferent discharges over these fibers vanish completely[80]. The gamma motoneurons are known to innervate the intrafusal muscle fibers of the muscle spindles and cessation of their tonic activity abolishes afferent discharges originating in the stretch receptors. Granit recently pointed out that the efferent activity of the gamma motoneuron system, being subject to supraspinal control, represents a sensitive indicator of the functional state of the reticular activating system[73]. It appears highly significant that the degree of activity in gamma motoneurons and in afferent fibers from muscle spindles is under a variety of circumstances paralleled by a concomitant degree of activation ("desynchronization," that is, low voltage-high frequency activity) of the electroencephalogram[59]. Whether this correspondence is indicative for the functional state of an arousal mechanism that controls central and efferent activity, or whether EEG activation is secondary to increased afferent drive from muscle spindles activated by the gamma motor system, cannot be decided at present. However, some of the behavior changes in animals (for example, reduction of motor activity) may be related to the blockade of the gamma motor system which, at least in some instances, has been shown to be the starting mechanism for movement[54]. Such considerations, in any case, stress the point that Chl.

has the potential to interfere with a variety of physiological activities and that it is, at present, difficult to decide whether any particular action by itself or the peculiar context of several actions of central or peripheral origin, or both, lead to the changes of normal and pathological behavior.

b) *Reserpine.* Reserpine did not alter the threshold for recruiting responses and EEG arousal in cats for periods up to 3 hours after intravenous injection of doses as high as 100 mg. per kg.[96]; the recovery of thalamic neurons, determined from responses in medial lemniscus and capsule, was also not affected by reserpine[97]: no similarity with the action of barbiturates could thus be established[94]. In curarized rabbits an activation of the electrocortiogram characteristic for alertness (low voltage, fast activity) was observed after administration of 1.5 to 2 mg. per kg.[135]. Suppression of slow wave and spindle burst activity in the electrocortiogram and depression of the recruiting response in nonanesthetized rabbits was also reported by Gangloff and Monnier[66].

Convulsive activity induced by reserpine in the limbic system of intact cats attracted considerable attention[96, 110]. Reserpine was, however, less active in producing convulsive activity of limbic structures by itself if the experiments were carried out in "encephale isole" preparations, but it prolonged evoked rhinencephalic seizures even under these conditions[149]; this again illustrates that the amount of existing afferent drive is able to determine the activity of centrally acting drugs. Such observations are significant for arriving at an understanding of the action of reserpine on behavior since the rhinencephalon is known to represent a pool into which afferent impulses of different sensory modalities enter[74]. Furthermore, it represents a structure in which convulsive activity is accompanied by such symptoms as "arrest reaction," reduced emotional expression and loss of contact with environment[3,91,110].

Reserpine facilitated the tonic extension phase of electrically or drug induced (pentylenetetrazol, caffeine) convulsions in mice[35] and antagonized the depressant effect of Dilantin upon the tonic extensor phase of electroshock convulsions[36]. However, monkeys made epileptic by prior application of aluminum cream to one hemisphere were rendered refractory to provocation of seizures by intense sensory stimulation (stick prodding)[38]. Also, audiogenic seizures were specifically suppressed in mice, the convulsive activity of picrotoxin and nicotine essentially remaining unaltered[166]. In spinal and decerebrated cats, Esplin and Heaton[56] found that reserpine (5 to 10 mg. per kg.) markedly reduced the post-tetanic potentiation in the monosynaptic pathway. Reserpine, in doses of 1.5 mg. per kg. intravenously, restored the "primary" auditory cortical responses to control levels, after they had been facilitated by LSD[132].

Additional aspects of the pharmacological actions of reserpine, such as origin and nature of the hypotensive activity, were exhaustively reviewed by Bein[11] and Wikler[175]. Reference will be made here only to a recent study by Dontas[52] in which reduction of the impulse traffic over the splanchnic nerves after administration of reserpine was demonstrated.

c) *Meprobamate.* In an attempt to develop mephenesin-like drugs with prolonged activity, it was found that the dicarbamates derived from 2-substituted 1,3-propanediols were potent anticonvulsants with prolonged duration of action[12]. The 2-methyl-2-n propyl substituted derivative (meprobamate) attracted attention for its

sedative action; in monkeys and rats the compound also prolonged the hexobarbital sleeping time, antagonized the convulsant action of pentylenetetrazole and strychnine, and prevented the occurrence of maximal electroshock seizures[13]. Meprobamate acted on the spinal cord essentially in the same way as mephenesin, that is, by depressing polysynaptic reflexes more than monosynaptic reflexes, but meprobamate differed from mephenesin with respect to electroencephalographic changes[81]: with increasing doses of meprobamate, high voltage-slow activity with occasional waxing-waning spindle bursts first appeared in the nucleus ventralis of the thalamus; subsequently, doubling of the voltage of cortical and quadrupling of the voltage of thalamic slow waves was noted (cats; 20 to 40 mg. per kg.). It has been pointed out that the actions of meprobamate are not too different from effects that could be obtained with barbiturates, alone or in combination with mephenesin[127].

d) *Azacyclonol.* Azacyclonol was not by itself effective in altering the spontaneous electrical activity of hypothalamus and the arousal function of the reticular formation; it was only after the reticular formation had been activated by previous administration of lysergic and diethylamide (LSD 25), or mescaline, that Azacyclonol restored the normal sleep pattern of the electrocortiogram. It appears that this drug only counteracts arousal produced by substances generally classified as "hallucinogens," but not arousal caused by other central stimulants[134].

Marazzi and Hart[111] used as a test the transcallosal two neuron pathway which is susceptible to partial block by mescaline. Not only azacyclonol but also Chl. and reserpine, if previously administered, protected the pathway from the depression by a subsequent dose of mescaline.

e) *Benactyzine.* The electroencephalographic changes caused by benactyzine in cats were essentially identical with the effects produced by atropine[14]: they consisted in the appearance of irregular bursts with a predominant frequency of 8 to 15 per sec. EEG arousal from sensory and thalamic stimulation was blocked, but recruiting responses invoked in the cortex by thalamic stimulation were not affected.

The hypnotic potency of hexobarbital was potentiated. With respect to a peripheral anticholinergic effect on smooth muscle organs, benactyzine was about twenty times more potent than chlorpromazine.

BIOCHEMICAL ASPECTS. a) *Chlorpromazine.* In the urine of dog and man the sulfoxide of Chl. was identified as its main metabolic product[143]. The sulfoxide was devoid of significant adrenergic blocking and central depressant activity in animals[117] and man[47].

Neither the respiration of cerebral cortex nor the capacity of cortical tissue to acetylate suitable subtrates was reduced in rats when doses of 10 to 50 mg. per kg. of Chl. were administered; an increase of the ATP level, indicative of decreased utilization of ATP, was observed, this effect having been most marked in the mid brain area[76]. However, if added to slices of brain cortex in media containing glucose, fructose, pyruvic or glutamic acid, Chl. at concentrations of 0.3 to 0.6 mM. depressed progressively respiration; this effect was not obtained in the presence of succinic acid[106a]. Like barbiturates, also Chl. inhibited the augmenting effect of potassium ions on the respiration of brain tissue. Most sensitive was the inhibition of glycine incorporation into brain proteins: this process was interfered with by Chl. at concentrations of 0.2 mM[106a]. Abood[1] found that Chl. uncoupled the oxidative phosphorylation of brain

mitochondria and inhibited cytochrome oxidase specifically. These results gained significance through the fact that the Chl. sulfoxide, which lacks significant central action, did not inhibit cytochrome oxidases[16]. Also, the oxidation of DPNH by a particulate preparation of brain mitochondria was strongly inhibited by Chl., but not by its sulfoxide[162a]. The turnover of phospholipids was depressed by Chl. (20 mg. per kg.) in brain tissue[4]. During administration of a daily dose of 100 mg., a significant increase of the beta globulin fraction was observed in man[165].

b) *Reserpine.* Reserpine labeled with C^{14} in the 4-methoxy group of the trimethoxy benzoic acid moiety of the molecule was used for the study of its distribution and excretion in mice following intravenous injection[145]. The drug disappeared rapidly from the blood stream, only 0.3% remaining there after 2 minutes following injection; radioactivity was demonstrated in various organs like spleen, liver and brain from where it was gradually eliminated over a period of 2 hours. Fat tissue, however, continued to take up labeled drug over a period of 6 hours following administration. There was no parallelism between the amount of reserpine present in the brain tissue and its curve of action[28]. High levels of methylreserpate were found in the rat after oral, but not after parenteral, administration of reserpine[68]; conversion to methylreserpate took place in the intestinal tract[67].

Reserpine reduced the uptake of radioactive methionine by the hippocampal area and the limbic system[110]. The drug depressed the oxygen consumption of brain tissue only in relatively high doses[133], but it increased the glycogen stores in lower doses[39]. Inhibition of the organic binding of I^{131} by thyroid slices was obtained when reserpine was added to the incubation medium (0.08 mg. per ml.)[114]. A marked effect of reserpine on the storage of diphosphopyridine nucleotide (DPN) in the liver of mice after administration of nicotinamide was reported by Burton *et al.*[32].

Investigations of Pletscher, Shore and Brodie[128] disclosed that reserpine released 5-hydroxytryptamine (serotonin) from various tissues, including brain; it took a period of several days to restore the serotonin level after administration of a single dose of reserpine. The liberated serotonin was excreted in the urine as indole acetic acid[146]. So far, only Rauwolfia alkaloids with sedative action have been found to liberate serotonin[129]. Pletscher *et al.*[128] furthermore observed that serotonin, if administered to mice in very large doses, increased the activity of hypnotics in the same way as reserpine did; the potentiating effect of both substances was counteracted by lysergic acid diethylamide (LSD)[147], which is also known to suppress the peripheral actions of serotonin and whose hallucinogenic action, for reasons of its chemical structure, is considered to be due to competitive antagonism with serotonin. Mono-amine oxidase activity of various parts of the brain was found to be greatest in these regions where serotonin concentration was highest[19]; serotonin is rapidly oxidized by preparations containing this enzyme[18] and this reaction is inhibited by iproniazid[180]. When mice, rats or rabbits were pretreated with iproniazid, it was seen that a subsequent dose of reserpine only produced excitation instead of the usual depression[37]. On the basis of these findings and other arguments not discussed here, the hypothesis was advanced that serotonin represented a central neurohumoral agent and that the action of reserpine was in some way mediated by serotonin

(*cf.*[29,179]). Objections against this hypothesis have, however, been raised: 2-brom-d-lysergic acid diethylamide (BOL 148), a potent antagonist of serotonin with respect to its smooth muscle stimulating activity[33,158] also antagonized the potentiation of the hexobarbital-sleeping time caused by either serotonin or reserpine, acting in this respect like LSD[142]; but BOL 148 does not produce hallucinations in man[33]. How complicated the issue is, can best be illustrated by a recent observation of Olds[123]: LSD inhibited self-stimulation in rats with implanted electrodes and this action of LSD was antagonized by serotonin if the electrode tips were located in the posterior hypothalamus; BOL 148 did not influence the stimulation rate in these cases. However, serotonin did not antagonize the LSD effect if the stimuli were applied to the anterior hypothalamus and BOL 148 acted in this case like LSD.

Serotonin is not the only tissue constituent liberated by reserpine, nor is reserpine the only agent that releases serotonin from brain tissue. Reserpine diminishes the noradrenalin content of the hypothalamus and releases medullary amines from innervated, but not from denervated, adrenal glands[88]; amphetamine lowers the concentration of serotonin in the brain[125]. Reserpine liberates histamine *in vivo* from blood[169].

CLINICAL PHARMACOLOGY. The evaluation of drug effects on human behavior, normal or pathologic, is made difficult by the fact that few relevant personality functions are accessible to objective measurement applicable to clinical studies in man. Communication in this field is hampered because concepts occurring in statements about human behavior often mean different things to different persons. Highly variable circumstances, such as biographical, environmental and psychosocial factors and the observer-patient interaction, are bound to influence and determine the effect of drugs on personality functions to a much higher degree than they do in any other instance of drug bioassay in man. These limitations have been lucidly discussed by Wikler[175] and motivated the Department of Health, Education and Welfare to issue "recommendations for reporting studies of psychiatric drugs"[167]. Another difficulty arises from the uncertainty of classification of psychiatric disorders and it was, therefore, suggested that drug effects be evaluated in terms of their influences on "target symptoms" rather than with reference to a specific clinical diagnosis[105].

a) *Chlorpromazine and other Phenothiazine derivatives.* Hamon *et al.*[79] and Delay, Deniker and Harl[49] were the first to report on the calming effect of Chl. in a group of patients with excitation and agitation, consisting of anxious and melancholic states, schizophrenia, delirium, hallucinations and obsessions. These observations were subsequently confirmed and extended by several investigators[69,98,176] who, in spite of wide differences in the conditions of carrying out the assay, essentially agreed that Chl. was effective in reducing psychomotor excitation of schizophrenic, manic-depressive and toxic origin. The efficacy of Chl. found an objective expression in the statement of Bird *et al.*[17] that, in their experience, physical restraint of patients was decreased by 74%, and ward accidents by 75%, since initiation of Chl. treatment. Less agreement exists with respect to the drug action on hallucinations, delusions and paranoid ideas in schizophrenic patients. Some attenuating action has been claimed[160], but Elkes and Elkes[55], in a careful study, stated that the ideational content of

delusions and hallucinations was not essentially altered, although the patients were emotionally less disturbed by it. Hallucinatory states of toxic psychoses, particularly as found in chronic alcoholics, however, subsided regularly after initiation of Chl. treatment[69]. The dereistic behavior of hebephrenic schizophrenics was largely drug resistant, but hyperkinetic excitement, if present, subsided during periods of drug administration. Some improvement was obtained in catatonic schizophrenics and even social recovery was reported in some cases; reduction of anxiety, disappearance of autonomic signs and reduction of stupor to the extent of initiation of verbalization and a reasonable degree of psychotherapeutic rapport were obtained. The periodic outbursts of agitation in senile and atherosclerotic patients were commonly controlled by Chl. Almost uniformly satisfactory results were reported in cases of psychoneuroses of the anxiety type, but, except for diminution of anxiety, poor results were generally obtained in depressive patients. The obsessive-compulsive type of psychoneuroses had obviously a better success rate concerning social rehabilitation but magical obsessive thinking, deprived of anxiety, persisted[141]. An area not yet fully explored, but with promising perspectives, lies in the field of behavior disorders of children where gain of weight and appetite, control of enuresis, lessening of hyperactivity and increase of sociability provide more objective scores for drug evaluation.

The attainment of good clinical results is determined by the dosage level and by the total length of time throughout which Chl. is administered. General agreement exists that an initial dose in the order of 200 mg. daily (oral or injected intramuscularly in individual doses of 50 mg. distributed over the day) represents a reasonable start of treatment in psychotic patients. Subsequently, continuation by oral route, with daily dose increments of 200 mg. are advised until the onset of what may be considered a specific therapeutic effect; 1600 to 2400 mg. per day are stated as upper limits of the relatively safe dose range[100,112]. A moderate degree of tolerance usually developed after periods of prolonged treatment, but habituation was not observed and sudden discontinuation was not followed by withdrawal symptoms[141]. A maintenance dose of 200 mg. per day may be useful in some cases[100]. For children of 9 to 12 years of age, a dose of 10 to 50 mg. t.i.d. was used[141].

The effects of Chl. on disturbances of behavior in epileptics were studied by Bonafede[20] in a group of 78 female patients while seizures were controlled to various degrees by anticonvulsant medication. Taking general quieting and gain of weight and appetite as scores, 41% were considered markedly improved and only 17% unaffected. In such studies, the lowering by Chl. of the sedation threshold with barbiturates[24] and a possible seizure provoking action of Chl.[162] must be taken into account.

Contrary to previous reports in the literature, Fraser and Isbell[64] found no significant reduction of the intensity of morphine-abstinence syndrome when Chl. was administered prior to and during the first 36 hours of abstinence (100 mg. intramuscularly or 800 mg. orally per day).

The behavioral actions of Chl. in man were frequently considered analogous to those of frontal lobotomy. The investigations of Petrie and LeBeau[126] on 111 patients after leukotomy, selective surgery of areas 9 and 10, and cingulectomy (areas 24 and 32) revealed, however, distinct differences: Chl. increased the scores for introver-

sion markedly and left those for intelligence unchanged, but opposite changes were obtained after leukotomy; only cingulectomy produced patterns of changes in these scores which were qualitatively comparable to those induced by Chl. Personality profiles, using The Wechsler-Bellevue intelligence scale, the Rohrschach test and the multidimensional scale for rating psychiatric patients (MSRPP)[109] were determined in a group of 20 chronic schizophrenics during Chl. treatment and compared with the corresponding values obtained in 20 patients receiving placebos[2]: Chl. significantly enhanced logical thinking without altering overall intellectual functions, anxiety and hostility to an extent different from the placebo effect; Chl. produced greater submissiveness and it was concluded that this indicated the need for rehabilitative procedures.

Out of a total of 425 patients studied in one series[141], 45% showed mild to moderate drowsiness and 30%, especially those on high doses, showed hypotension. A fall of peripheral resistance with a variable effect on cardiac output and no evidence of renal hemodynamic alterations had previously been observed in man and dogs[118]. Mild elevation of body temperature occurred in 3% of the abovementioned group of patients and jaundice occurring during treatment with Chl. were well described by Cohen and Archer[40] and by Stacey *et al.*[159], and there is now general agreement that it is of an obstructive type due to a cholangiolitic hepatitis as manifestation of a drug sensitivity[72]. The overall incidence of jaundice in patients receiving Chl. is estimated 1.5%[72]. Allergic skin eruptions and rare cases of fatal agranulocytosis were also reported[84]. The development of parkinsonism is frequent in patients on large doses and its incidence is estimated to be about 15%[99]; treatment with benztropine methane sulfate (Cogentine) was found to control this complication effectively.

Promazine, different from chlorpromazine only by lacking the Cl substituent on the phenothiazine ring, was administered to 100 chronic psychotic female patients presenting a variety of symptoms[63]. Daily doses up to 2 gm. were administered by mouth and no untoward effects were noted. Combativeness, uncooperativeness and noisy behavior were best controlled by the drug (40% or higher success rates), whereas hallucinations, idleness, negativism and hostility were the least controllable target symptoms (success rates 7 to 8%).

The compounds Campazine, Trilafon and Vesprin, listed under STRUCTURE-ACTIVITY RELATIONSHIP exerted their therapeutic activity in a series of over 1,000 patients at considerably lower dose levels than either Chl. or Promazine. This may have been responsible for the lower incidence of side reactions, especially for the absence of jaundice and hematological disorders[70]. The profile of personality changes induced by these drugs in chronic psychotic patients was distinctly different from that encountered during the treatment with Chl. and Promazine. Resolution of delirium, hallucinations and delusions could in most patients be achieved with little or no accompanying sedation. Depending on the dosage schedule, the patients may pass through a phase of "turbulence" which may lead to rejection of the drug or avoidance of treatment. Parkinsonism was frequently observed in this series, but it could be controlled by appropriate medication of Cogentine.

b) *Reserpine.* General agreement exists that reserpine in sufficient dose and administered over a sufficient period of time, can reduce or abolish agi-

tation, tension, anxiety and combativeness in disturbed psychotic patients[102,141]. As in the case of Chl., delusions and hallucinations frequently retain their content, but the patients are made less anxious by it and they become capable to talking about it as if it were the idea of a third person[85]. In contrast with Chl., reserpine was occasionally found to produce or aggravate depressive symptoms[99,171], which outlasted the period of drug administration and in some cases caused suicidal tendencies[104]. Electroshock treatment, administration of iproniazid (50 mg., t.i.d.)[141] or methylphenidate (Ritalin)[62] improved the drug-induced depression. Barsa and Kline[6,103] delineated three distinct phases during prolonged administration of reserpine: a "sedative" phase was evident within the first few days of treatment; assaultive, agitated, resistive and overactive patients became quiet, cooperative and appeared in good contact with their environment. This phase was followed at the end of the first week of treatment, by a "turbulent" phase: hallucinations and delusions increased and psychotic symptoms, which may have been latent prior to treatment, became frequently florid. The duration of this period may be restricted to a few hours, but more frequently it lasted as long as 2 to 3 weeks. The dizziness and feeling of strangeness characteristic for the "turbulent phase" usually began to subside during the second or third week of treatment, which then was followed by the "integrative phase" in which a closer contact to environment was established and in which delusions and hallucinations seemed to subside. Chlorpromazine was successfully used as an adjunct to the reserpine treatment during the "turbulent" phase[8]. More recently, Barsa and Kline[9] pointed out that in the course of treatment with reserpine, alone or in combination with Chl., complaints occurred frequently about "jittery" feelings, draining of affect ("anhedonia") and mental retardation even if clinical improvement of some "target" symptoms was obtained; such symptoms did not arise when Chl. was used alone.

Considerable variation exists with respect to the dosage schedule used by different observers. Doses in the order of 1.0 mg. per day are considered as "sedative doses;" for the treatment of psychotic conditions doses of 10 to 15 mg. per day were recommended by Kline[104] and evaluation of a possible therapeutic effect should not be made earlier than after 1½ to 4 months of continuous drug administration. A maintenance dose of 3.0 to 6.0 mg. per day or occasional booster doses are recommended for the follow-up period. The best therapeutic effect was occasionally seen on abrupt discontinuation of an intensive treatment schedule[104].

The inherent difficulty of numerical evaluation of the success rate of treatment in this area is indicated by a review of Freeman[65] who listed average rates of social or complete remission in schizophrenic patients as reported by different observers: such results can be expected in 19% with custodial and supportive treatment alone, in 22% with reserpine, in 34% with Chl., and in 48% with insulin coma therapy; but no statements on remission were made and the material is heterogenous with respect to duration of the disease, previous treatment, age distribution, severity and dosage schedule. In another series of 150 chronically disturbed psychotics who had failed on electroshock or insulin shock, or both, treatment, 84% showed some improvement and 21% could leave the hospital[103]; they were treated with doses similar to the ones stated before. Rosner *et al.*[138] undertook a double-blind placebo con-

trolled study on 84, mostly schizophrenic, patients comparing the results of a 30-day course of treatment with reserpine in low doses (2 mg. per day), Chl. (100 mg. per day) and phenobarbital (120 mg. per day); critical flicker fusion frequency, scores on a manifest symptom inventory and ratings on an anxiety scale were determined. The scores on the manifest symptom inventory were significantly reduced by placebo and drugs, but no statistically significant difference was noted between the effect of placebos and the different drugs in the comparatively small doses used; ratings on the anxiety scale were reduced by all treatments except phenobarbital. Reserpine produced the most marked increase of body weight which was interpreted as a manifestation of an anxiety-reducing effect; only reserpine reduced the flicker fusion frequency. A distinct difference in the susceptibility to reserpine treatment was noted in two groups of psychotic patients according to their responsiveness to electroshock: out of 82 patients who maintained contact with the environment as long as they were given intermittent convulsive treatment, 71 patients improved on reserpine therapy and 59 patients could be discharged; but in a group of 139 shock-resistant patients, only 52 improved and 19 were eligible for discharge[163].

Gratifying results were obtained by Sainz[149] in geriatric psychotics with doses of reserpine ranging from 3.0 to as high as 130.0 mg. per day: in a group of 48 querulous, demanding and hostile patients, remissions were obtained in 40 cases. Severe alcoholic delirium tremens was favorably influenced by reserpine in doses of 2.5 mg. (intramuscularly or intravenously) repeated after 3 to 4 hours and again if necessary[5].

The potential usefulness of reserpine in the treatment of psychoneuroses is far from being established. A reduction of anxiety with slow onset, often requiring 2 to 3 months for development, was observed by Smith[154] using a dosage schedule of 1.0 to 3.0 mg. per day; depressive trends were occasionally exacerbated. Kline[103] assumes that reserpine, in neurotics as well as in psychotics, provides conditions for a reorganization of the personality structure by breaking up fixed reaction patterns, psychosomatic conversion symptoms or detachment, thus setting the stage for successful psychotherapy.

The most commonly encountered side effects were generalized tremulousness, occasionally accompanied by muscular sensations ("like small electric shocks"), hypotension, drowsiness, fatigue, nasal stuffiness, intestinal cramps and diarrhea; menstrual irregularities, lessening of sexual drive and lowered resistance to infectious diseases were also described. About 5% of the patients undergoing more vigorous treatment developed a typical Parkinsonian syndrome[9]. An increase in seizure frequency during the initial phase of reserpine treatment was noted in psychotic patients with convulsive disorders[7].

c) *Azacyclonol.* Fabing[60] observed that azacyclonol suppressed hallucinations induced by LSD and mescaline and suggested the term "ataraxy" (namely, freedom from confusion) to characterize this type of action. Subsequently, improvement was reported in cases of acute and chronic schizophrenia, alcoholic psychosis and in some patients with postoperative hallucinations, disorientation and disturbances of thought and mood[61]. Further studies by Rinaldi *et al.*[136,137] lead to the conclusion that azacyclonol (10 mg. twice daily) acted mainly by mitigating hallucinations, delusions and illogical thinking. Comparison with

reserpine (2 mg., b.d.) and Chl. (200 mg., b.d.) was carried out in the same group of patients and it was stated that the three drugs did not produce equivalent degrees of improvement in individual patients: reserpine acted more by a general quieting effect and Chl. mainly by reducing all manifestations of behavior. Any improvement that was caused during the administration of azacyclonol gave way to the original status when the drug was substituted by placebos. Alcoholic hallucinosis also responded to treatment with azacyclonol[131]. But Lemere[106] did not observe beneficial effects with azacyclonol in hallucinatory states of different origin. No clinical side effects were reported after administration of doses up to 300 to 400 mg. per day.

d) *Benactyzine*. The emotional reaction of normal and psychoneurotic persons subjected to verbal stimuli were determined by measuring skin resistance, skin temperature, pulse rate and respiration. Emotional responses, present in the control situation, were markedly reduced after drug administration[92]. The reduction of emotional reactivity to stress was also noted by Kinross-Wright and Moyer[101] in 42 patients suffering from a variety of psychiatric disorders, but there was a considerable incidence of undesirable side effects, such as palpitations, constipation, pupillary dilation, and dryness of the mouth. Occasionally, feelings of depersonalization and confusion of thought were reported. These symptoms were also experienced by some normal volunteers and are largely explicable on the basis of the atropine-like action of benactyzine[14,31]. No major changes in neurotic patterns of thinking and behavior were observed.

e) *Meprobamate*. The first clinical reports were based on observations made on psychoneurotic patients in an office practice: with doses of 400 to 2,400 mg. per day, reduction of tenseness, restlessness, cardiac palpitations and hyperhidrosis were noted[22]. Tension headache and psychosomatic pain were also found to improve[144], but the conditions under which these trials were carried out may not have been satisfactory for the evaluation of a specific drug effect. Subsequent and more extensive studies resulted in determining the types of personality disorders in which some benefit could be obtained from the use of meprobamate. These were: psychoneurotic anxiety states in which tension played a prominent role[71,124], and apprehension, agitation, guilt feelings and sleeplessness of chronic alcoholics[75,164]. Some useful sedative effects were also obtained in patients with senile psychosis and this action facilitated their management[23]. The value of meprobamate in chronic schizophrenic patients was essentially limited to a mild sedative and anxiety relieving effect[86]. No psychological improvement was obtained in psychotic patients (1.6 to 4.0 gm. per day), but 12 out of 17 schizophrenic patients improved after one month while receiving 150 mg. Chl. combined with 1,600 mg. meprobamate daily: the same patients had previously neither responded to Chl. alone nor to reserpine[10]. One single attack of convulsions was noted in 6 out of 25 schizophrenic patients following abrupt withdrawal of meprobamate after it had been administered in a dose of 2.4 gm. daily for 9 months.

Meprobamate was found useful for the management of patients with acute active poliomyelitis of the spinal type, possibly due to its combined sedative and weak muscle relaxing effect[51]. The latter action was verified in man by means of electromyographic studies[50] and was claimed to be beneficial in the treatment of skeletal muscle spasms due to rheumatic[157] and various other conditions[53].

REFERENCES

(1) **Abood, L. G.:** Proc. Soc. Exper. Biol. & Med., **88,** 688, 1955. (2) **Abrams, J.:** Dis. Nerv. Sys., **19,** 20, 1958. (3) **Andy, O. R.,** and **Akert, K.:** J. Neuropathol. & Exper. Neurol., **14,** 198, 1955. (4) **Ansell, G. B.,** and **Dohmen, H.:** J. Neurochemistry, **1,** 150, 1956. (5) **Avel, M.,** and **Vogel, P. J.:** J. Am. Med. Assn., **159,** 1516, 1955.

(6) **Barsa, J. A.,** and **Kline, N. S.:** J. Am. Med. Assn., **158,** 110, 1955. (7) Iidem: A.M.A. Arch. Neurol. & Psychiat., **74,** 31, 1955. (8) Iidem: Ibid., **74,** 280, 1955. (9) Iidem: Ibid., **76,** 90, 1956. (10) Iidem: Am. J. Psychiat., **112,** 1023, 1956. (11) **Bein, H. J.:** Pharmacol. Rev., **8,** 435, 1956. (12) **Berger, F. M.:** J. Pharmacol. & Exper. Therap., **104,** 229, 1952. (13) Idem: Ibid., **112,** 413, 1954. (14) **Berger, F. M., Hendley, C. D.,** and **Lynes, T. E.:** Proc. Soc. Exper. Biol. & Med., **92,** 563, 1956. (15) **Berkun, M. M.,** quoted by **Miller, N. E.:** Ann. New York Acad. Sci., **65,** 318, 1956. (16) **Bernsohn, J., Namajuska, J.,** and **Cochrane, L. S. G.:** Proc. Soc. Exper. Biol. Med., **92,** 201, 1956. (17) **Bird, E. G., Goss, J. D., and Denber, H. C.:** Am. J. Psychiat., **111,** 930, 1955. (18) **Blaschko, H.:** Pharmacol. Rev., **4,** 415, 1952. (19) **Bogdanski, D. F.,** and **Udenfried, S.:** J. Pharmacol. & Exper. Therap., **116,** 7, 1956. (20) **Bonafede, V. J.:** A.M.A. Arch. Neurol. & Psychiat., **74,** 158, 1955. (21) **Bonvallet, M., Dell, P.,** and **Hiebel, G.:** EEG Clin. Neurophysiol., **6,** 119, 1954. (22) **Borrus, J. C.:** J. Am. Med. Assn., **157,** 1596, 1955. (23) **Bower, W. H.:** Ann. New York Acad. Sci., **67,** 801, 1957. (24) **Bradley, P. B.,** and **Jeavous, J. M.:** EEG Clin. Neurophysiol., **9,** 661, 1957. (25) **Bradley, P. B.,** and **Hance, A. J.:** Ibid., **9,** 191, 1957. (26) **Brady, J. V.,** and **Nauta, W. J. M.:** J. Comp. & Physiol. Psychol., **46,** 339, 1953. (27) **Brady, J. V.:** Science, **123,** 1033, 1956. (28) **Brodie, B. B., Pletscher, A.,** and **Shore, P. A.:** Science, **122,** 968, 1955. (29) **Brodie, B. B.,** and **Shore, P. A.:** *in* "Hormones, Brain Function and Behavior," Ed. H. Hoagland, New York: Academic Press, 1957. (39) **Brown, B. B., Braun, D. L.,** and **Feldman, R. G.:** J. Pharmacol. & Exper. Therap., **118,** 153, 1956. (31) **Burtner, R. B.,** and **Cusic, J. W.:** J. Am. Chem. Soc., **65,** 262, 1943. (32) **Burton, R. M., Kaplan, N. O., Goldin, A., Leitenberg, M., Humphreys, S. R.,** and **Sodd, M. A.:** Science, **127,** 30, 1958.

(33) **Cerletti, O.,** and **Rothlin, E.:** Nature, London, **176,** 785, 1955. (34) **Chatterjee, A., Patrashi, S. C.,** and **Werner, G.:** Progress Chem. Org. Nat. Prod., **13,** 346, 1956. (35) **Chen, G., Ensor, C. R.,** and **Bohner, B.:** Proc. Soc. Exper. Biol. & Med., **86,** 507, 1954. (36) **Chen, G.,** and **Ensor, C. R.:** Ibid., **87,** 602, 1954. (37) **Chessin, M., Kramer, E. R.,** and **Scott, C. C.:** J. Pharmacol. & Exper. Therap., **119,** 453, 1957. (38) **Chusid, J. B., Kopeloff, L. M.,** and **Kopeloff, N.:** Proc. Soc. Exper. Biol. & Med., **88,** 276, 1955. (39) **Claus, J. L.:** Quoted from **Schneider, J. A.,**[152]. (40) **Cohen, J. M.,** and **Archer, J. D.:** J. Am. Med. Assn., **159,** 99, 1955. (41) **Cook, L., Weidley, E. F., Morris, R. W.,** and **Mattis, P. A.:** J. Pharmacol. & Exper. Therap., **113,** 11, 1955. (42) **Cook, L.,** and **Weidley, E.:** Ann. New York Acad. Sci., **66,** 740, 1957. (43) **Courvoisier, S., Fournel, J., Ducrot, R., Kolsky, M.,** and **Koetschet, P.:** Arch. Int. Pharmacodyn., **92,** 305, 1953.

(44) **Das, N. N.,, Das Gupta, S. R.,** and **Werner, G.:** Arch. Int. Pharmacodyn., **99,** 451, 1954. (45) **Das Gupta, S. R., Mukherjee, K. L.,** and **Werner, G.:** Ibid., **97,** 149, 1954. (46) **Das Gupta, S. R.,** and **Werner, G.:** Ibid., **100,** 409, 1955. (47) **Davidson, J. D., Terry, L. L.,** and **Sjoerdsma, A.:** J. Pharmacol. & Exper. Therap., **121,** 8, 1957. (48) **Dews, P. B.:** Ann. New York Acad. Sci., **65,** 268, 1956. (49) **Delay, J., Deniker, P.,** and **Harl, J. M.:** Ann. Méd. Psychol., **110,** 267, 1952. (50) **Dickel, A. H., Wood, J. A.,** and **Dixon, H. H.:** Ann. New York Acad. Sci., **67,** 780, 1957. (51) **Dixon, M. N.:** Ibid., **67,** 772, 1957. (52) **Dontas, A. S.:** J. Pharmacol. & Exper. Therap., **121,** 1, 1957.

(53) **Eisenberg, S. H.,** and **Neviaser, J. S.:** Ann. New York Acad. Sci., **67,** 853, 1957. (54) **Eldred, E., Granit, R.,** and **Merton, P. A.:** J. Physiol., **122,** 498, 1953. (55) **Elkes, J.,** and **Elkes C.:** Brit. Med. J., **2,** 560, 1954. (56) **Esplin, D. W.,** and **Heaton, D. G.:** J. Pharmacol. & Exper. Therap., **121,** 267, 1957. (57) **Essig, C. F.,** and **Carter, W. W.:** Proc. Soc. Exper. Biol. & Med., **95,** 726, 1957. (58) **Estes, W. K.,** and **Skinner, B. F.:** J. Exper. Psychol., **29,** 390, 1941. (59) **von Euler, C.,** and **Soderberg, U.:** Experientia, **12,** 278, 1956.

(60) **Fabing, H. D.:** Neurology, **5**, 319, 1955. (61) **Fabing, H. D.,** and **Hawkins, J. R.:** Dis. Nerv. Sys., **16**, 329, 1955. (62) **Ferguson, J. T.:** Ann. New York Acad. Sci., **61**, 101, 1955. (63) **Frain, M. K.:** J. Nerv. & Ment. Dis., **125**, 529, 1957. (64) **Fraser, H. F.,** and **Isbell, H.:** A.M.A. Arch. Neurol. & Psychiatry, **76**, 257, 1956. (65) **Freeman, H.:** New England J. Med., **255**, 877, 1956.

(66) **Gangloff, H.,** and **Monnier, M.:** Experientia, **11**, 404, 1955. (67) **Glazko, A. J., Dill, W. A., Wolf, L. M.,** and **Kazenko, O.:** Fed. Proc., **14**, 58, 1955. (68) Iidem: J. Pharmacol. & Exper. Therap., **118**, 377, 1956. (69) **Goldman, D.:** J. Am. Med. Assn., **157**, 1274, 1955. (70) Idem: Am. J. Med. Sci., **235**, 67, 1958. (71) **Gordner, A.:** Am. J. Psychiat., **114**, 524, 1957. (72) **Graham, G. S.:** Brit. Med. J., **2**, 1080, 1957. (73) **Granit, R.:** 1st Internat. Congress of Neurological Sci., p. 63, 1957. (74) **Green, J. D.,** and **Adey, W. R.:** EEG Clin. Neurophysiol., **8**, 245, 1956. (75) **Greenberg, L. A., Lester, D., Dora, A., Greenhouse, R.,** and **Rosenfeld, J.:** Ann. New York Acad. Sci., **67**, 816, 1957. (76) **Grenell, R. G., Mendelson, J.,** and **MacElroy, W. D.:** A.M.A. Arch. Neurol. Psychiatry, **73**, 347, 1955. (77) **Goody, W.:** Brain, **79**, 167, 1956. (78) **Guha, G., Das Gupta, S. R.,** and **Werner, G.:** Bull. Calcutta School Trop. Med., **2**, 46, 1954.

(79) **Hamon, J., Paraire, J.,** and **Velluz, J.:** Ann. Méd. Psychol., **110**, 331, 1952. (80) **Henatsch, H. D.,** and **Ingvar, D. H.:** Arch. Psychiatrie, **195**, 77, 1956. (81) **Hendley, C. D., Lynes, T. E.,** and **Berger, R. M.:** Proc. Soc. Exper. Biol. & Med., **87**, 608, 1954. (82) **Hess, E. H.:** Ann. New York Acad. Sci., **67**, 724, 1957. (83) **Himwich, H. E.,** and **Rinaldi, F.:** *in* "Brain Mechanisms and Drug Action," Edited by **Fields, W. F.** Springfield, Ill.: Charles C Thomas, 1957. (84) **Hodges, H. H.,** and **Lazerte, G. D.:** J. Am. Med. Assn., **158**, 114, 1955. (85) **Hoffman, J. L.,** and **Konchegul, L.:** Ann. New York Acad. Sci., **61**, 144, 1955. (86) **Hollister, L. E., Elkins, H., Hiler, E. G.,** and **Pierre, R. S.:** Ibid., **67**, 789, 1957. (87) **Holten, C. H.,** and **Sonne, E.:** Acta pharmacol. et toxicol., **11**, 148, 1955. (88) **Holzbaure, M.,** and **Vogt, M.:** J. Physiol., **131**, 617, 1956. (89) **Hunt, H. F.:** Ann. New York Acad. Sci., **65**, 258, 1956. (90) Idem: Ibid., **67**, 712, 1957. (91) **Hunter, J.:** EEG Clin. Neurophysiol., **2**, 193, 1950.

(92) **Jacobsen, E., Kehlet, H., Larsen, V., Munkvad, J.,** and **Skinhoj, K.:** Acta psychiat. & neurol. Scandinav., **30**, 607, 1955. (93) **John, E. R., Wenzel, B. M.,** and **Tschirgi, R. D.:** Science, **127**, 25, 1958.

(94) **King, E. E., Naquet, R.,** and **Magoun, H. W.:** J. Pharmacol. & Exper. Therap., **113**, 31, 1955. (95) **King, E. E.:** Ibid., **116**, 404, 1956. (96) **Killam, E. K.,** and **Killam, K. F.:** J. Pharmacol. & Exper. Therap., **116**, 35, 1956. (97) Iidem: *in* "Brain Mechanisms and Drug Action," Springfield, Ill.: Charles C Thomas, 1957. (97a) Iidem: Psychopharmacology, Edit. **H. H. Pennes,** (Progress in Neurobiology, Vol. III). New York: Hoeber-Harper, 1958. (98) **Kinross-Wright, V.:** Am. J. Psychiatry, **111**, 907, 1955. (99) Idem: Ann. New York Acad. Sci., **61**, 174, 1955. (100) Idem: Psychopharmacology Pub., **42**, Am. Assn. Adv. Sci., 1956. (101) **Kinross-Wright, V.,** and **Moyer, J. H.:** Am. J. Psychiat., **114**, 73, 1957. (102) **Kline, N. S.:** Ann. New York Acad. Sci., **59**, 107, 1954. (103) Idem: Psychopharmacology Pub., No. 42, Am. Assn. Adv. Sci., Washington, 1956. (104) Idem: Communication to Res. Assn. Nerv. Ment. Dis., New York, Dec. 1957. (105 **Kline, N. S.,** and **Stanley, A. M.:** Ann. New York Acad. Sci., **61**, 85, 1955.

(106) **Lemere, F.:** Am. J. Psychiat., **113**, 840, 1957. (106a) **Linden, O., Quastel, J. H.,** and **Sved, S.:** Psychopharmacology, Edit. **H. H. Pennes,** (Progress in Neurobiology, Vol. III). New York: Hoeber-Harper, 1958. (107) **Loewe, S.:** Arch. Int. Pharmacodyn., **108**, 453, 1956. (108) **Longo, V. G., von Berger, G. B.,** and **Bovet, D.:** J. Pharmacol. & Exper. Therap., **111**, 349, 1954. (109) **Lorr, M.:** Vet. Admin. Techn. Bull., **10**, 507, 1953.

(110) **MacLean, P. D., Flanigan, S., Flynn, J. P., Kim, C.,** and **Stevens, J. R.:** Yale J. Biol. & Med., **28**, 380, 1955. (111) **Marazzi, A. S.,** and **Hart, E. R.:** Symposium on Tranquilizing Drugs, Washington: Am. Assn. Adv. Sci., 1957. (112) **Margolis, L. H., Fischer, O., Butler, R. N.,** and **Simon, O.:** Psychopharmacology. (Ed. **N. S. Kline**), Pub. 42, Washington: Am. Assn. Adv. Sci., 1956. (113) **Mason, J. W.,** and **Brady, J. V.:** Science, **124**, 983, 1956. (114) **Mayer, S. W., Kelly, F. M.,** and **Morton, M. E.:** J. Pharmacol. & Exper. Therap., **117**, 197, 1956. (115) **Miller, R.**

A., Murphy, J. V., and **Mirsky, J. A.:** A.M.A. Arch. Neurol. & Psychiat., **78,** 526, 1957. (**116**) Iidem: J. Pharmacol. & Exper. Therap., **120,** 379, 1957. (**117**) **Moran, N. C.,** and **Butler, W. M.:** Ibid., **118,** 328, 1956. (**118**) **Moyer, J. H., Kent, B., Knight, R., Morris, G., Huggins, R.,** and **Handley, C.:** Am. J. Med. Sci., **227,** 283, 1954. (**119**) **Mukherjee, B.:** J. Sci. Industr. Res., 14A, Supplement, 1955.

(120) **Norton, S.,** and **de Beer, E. J.:** Ann. New York Acad. Sci., **65,** 249, 1956

(121) **Olds, J.:** Nebraska Symposium on Motivation (Ed.: **M. R. Jones**), Lincoln: Univ. of Nebraska Press, 1955. (**122**) **Olds, J., Killam, K. F.,** and **Bach-y-Rita, P.:** Science, **124,** 265, 1956. (**123**) Iidem: Ibid., **127,** 315, 1958. (**124**) **Osinski, W. D.:** Ann. New York Acad. Sci., **67,** 766, 1957.

(125) **Paasonen, M. K.,** and **Vogt, M.:** J. Physiol., **131,** 617, 1956. (**126**) **Petrie, A.,** and **LeBeau, J.:** J. Clin. Psychopathol., **17,** 170, 1956. (**127**) **Pfeiffer, C. C., Riopelle, A. J., Smith, R. P., Jenney, E. H.,** and **Williams, H. L.:** Ann. New York Acad. Sci., **67,** 734, 1957. (**128**) **Pletscher, A., Shore, P. A.,** and **Brodie, B. B.:** J. Pharmacol. & Exper. Therap., **116,** 46, 1956. (**129**) Iidem: Science, **123,** 992, 1956. (**130**) **Preston, J. B.:** J. Pharmacol. & Exper. Therap., **118,** 100, 1956. (**131**) **Procter, R. C.,** and **Odland, T.:** Dis. Nerv. Sys., **17,** 25, 1956. (**132**) **Purpura, D. P.:** A.M.A. Arch. Neurol. & Psychiat., **75,** 122, 1956.

(133) **Rau, G. C., Eisenbrandt, L. L., Paradise, R. R.,** and **Auyong, T. K. H.:** Fed. Proc., **14,** 381, 1955. (**134**) **Rinaldi, F.,** and **Himwich, M. E.:** Science, **122,** 198, 1955. (**135**) Iidem: Ann. New York Acad. Sci., **61,** 27, 1955. (**136**) **Rinaldi, F., Rudy, L. H.,** and **Himwich, H. E.:** Am. J. Psychiat., **112,** 343, 1955. (**137**) Iidem: Ibid., **112,** 678, 1955. (**138**) **Rosner, H., Levine, S., Hess, H.,** and **Kaye, H.:** J. Nerv. & Ment. Dis., **122,** 505, 1955. (**139**) **Rutledge, L. T.,** and **Doty, R. W.:** Am. J. Physiol., **191,** 189, 1957.

(140) **Sainz, A. A.:** Ann. New York Acad. Sci., **61,** 72, 1955. (**141**) Idem: Psychopharmacology, Pub. 42, Am. Assn. Adv. Sci., **1956.** (**142**) **Salmoiraghi, G. C.,** and **Page, J. H.:** J. Pharmacol. & Exper. Therap., **120,** 20, 1956. (**143**) **Salzman, N. P.,** and **Brodie, B. B.:** Ibid., **118,** 46, 1956. (**144**) **Selling, L. S.:** J. Am. Med. Assn., **157,** 1594, 1955. (**145**) **Sheppard, H., Lucas, R. C.,** and **Tsien, W. M.:** Arch. Int. Pharmacodyn., **103,** 256, 1955. (**146**) **Shore, P. A., Silver, S. L.,** and **Brodie, B. B.:** Science, **122,** 284, 1955. (**147**) Iidem: Experientia, **11,** 272, 1955. (**148**) **Sidman, M.:** Ann. New York Acad. Sci., **65,** 282, 1956. (**149**) **Siggs, E. B.,** and **Schneider, J. A.:** EEG Clin. Neurophysiol., **9,** 419, 1957. (**150**) **Schlittler, E.:** *in* "Rauwolfia," Boston: Little, Brown & Co., 1957. (**151**) **Schneider, J. A.,** and **Earl, A. E.:** Fed. Proc., **13,** 130, 1954. (**152**) **Schneider, J. A., Plummer, A. J., Earl, A. E.,** and **Gaunt, R.:** Ann. New York Acad. Sci., **61,** 17, 1955. (**153**) **Schwartzbaum, J. S.:** Proc. Soc. Exper. Biol. & Med., **90,** 275, 1955. (**154**) **Smith, S. K.:** Ann. New York Acad. Sci., **61,** 206, 1955. (**155**) **Smith, R. P., Wagman, A. I.,** and **Riopelle, A. J.:** J. Pharmacol. & Exper. Therap., **117,** 136, 1956. (**156**) **Smith, R. P., Wagman, A. I., Wagman, W., Pfeiffer, C. C.,** and **Riopelle, A. J.:** Ibid., **119,** 317, 1957. (**157**) **Smith, R. T.:** Ann. New York Acad. Sci., **67,** 839, 1957. (**158**) **Sollero, L., Page, J. H.,** and **Salmoiraghi, G. C.:** J. Pharmacol. & Exper. Therap., **117,** 10, 1956. (**159**) **Stacey, C. H., Azima, H., Huestis, D. W., Howlet, J. G.,** and **Hoffman, M. M.:** Canadian Med. Assn. J., **73,** 386, 1955. (**160**) **Stahelin, J. E.,** and **Keilholz, P.:** Schweiz med. Wschr., **83,** 581, 1955. (**161**) **Stein, L.:** Science, **124,** 1082, 1956. (**162**) **Stewart, L. F.:** EEG Clin., Neurophysiol., **9,** 427, 1957. (**162a**) **Strecker, H. J.:** Psychopharmacology, Edit. **H. H. Pennes,** (Progress in Neurobiology, Vol. III). New York: Hoeber-Harper, 1958.

(163) **Tasher, D. C.,** and **Chermak, M. W.:** Ann. New York Acad. Sci., **61,** 108, 1955. (**164**) **Thieman, J.,** and **Gauthier, J. W.:** Quart. J. Studies Alc., **17,** 19, 1956. (**165**) **Trigos, G.,** and **McCulloch, W.:** Dis. Nerv. Sys., **16,** 309, 1955. (**166**) **Tripod, J., Bein, H. J.,** and **Meier, R.:** Arch. Int. Pharmacodyn., **96,** 406, 1954.

(167) U.S. Public Health Service: Public Health Reports, **72,** 7, 1957.

(168) **Viaud, P.:** J. Pharmacy Pharmacol., **6,** 361, 1954.

(169) **Waalkes, T. P.,** and **Weissbach, H.:** Proc. Soc. Exper. Biol. & Med., **93,** 396, 1956. (**170**) **Walaszek, E. J.,** and **Abood, L. G.:** Science, **124,** 440, 1956. (**171**) **Weber, E.:** Schweiz. med. Wchnschr., **34,** 968, 1954. (**172**) **Weiskrantz, L.,** and **Wilson, W. A.:** Ann. New York Acad. Sci., **61,** 36, 1955. (**173**) **Werner, G.:**

Ann. Report, Conselho Nacional de Pesquisas, Rio de Janeiro, Brazil, 1957. (174) **Werner, G.:** Klin. Wchnschr., **36**, 404, 1958. (175) **Wikler, A.:** The Relations of Psychiatry to Pharmacology. Baltimore: The William & Wilkins Co., 1957. (176) **Winkelman, N. W.:** J. Am. Med. Assn., **155**, 18, 1954. (177) **Winter, A. A.,** and **Flataker, L.:** J. Pharmacol. & Exper. Therap., **101**, 156, 1951. (178) **Woodson, R. E., Youngken, H. W., Schlitler, E.,** and **Schneider, J. A.:** Rauwolfia, Boston: Little, Brown & Co., 1957. (179) **Woolley, D. W.:** *in* "Hormones, Brain Function and Behavior," Ed. H. Hoagland, New York: Academic Press, 1957.
(180) **Zeller, E. O.,** and **Barsky, J.:** Proc. Soc. Exper. Biol. & Med., **81**, 459, 1952. (181) **Zimbardo, P. G.,** and **Barry, H.:** Science, **124**, 84, 1958.

SUMMARIO IN INTERLINGUA

(See page 624 for original article)

Pneumonopathia Eosinophilic (Syndrome De Loeffler) Reporto De Un Caso, Describente Duo Attaccos In Le Mesme Patiente E Ponente In Contrasto Therapia Steroid Con Therapia Nonsteroide

Un veterano militar habeva duo attaccos de pneumonopathia eosinophilic (syndrome de Loeffler): Le prime in 1955 quando ille serviva in Japon, le secunde in 1958 quando ille visitava un collegio. Se presentava le opportunitate de comparar le attacco de 1958, que esseva tractate a bon successo per medio de hydrocortisona, con le attacco quasi identic de 1955, que non esseva tractate con steroide. Le attacco de 1955 permitteva observar le historia natural del morbo in iste patiente. Ille relatava nulle historia de allergia—personal o familial—que haberea potite causar le attaccos. Ambe episodios sequeva moderate exhaustion physic con exposition a un tempore inclemente que causava infectiones supero-respiratori tosto resultante in affection del bronchos e del parenchyma pulmonar.

RADIOLOGY

UNDER THE CHARGE OF

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ROENTGENOGRAPHIC SIGNS OF PULMONARY ARTERY OCCLUSION

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THE frequency of pulmonary embolism and infarction discovered at necropsy is matched by the surprisingly frequent failure to recognize the characteristic radiographic signs, which, either alone or in combination, should suggest the diagnosis. Review of films of many necropsy-proven cases and clinically proven cases (if one accepts the history of postoperative sudden pleuritic pain associated with radiographic changes and hemoptysis as being reasonably conclusive) reveals a preponderance of such diagnoses as "pneumonia," "postoperative pneumonia," postoperative pneumonitis," "postoperative atelectasis," "aspiration pneumonia" or "pneumonitis" and such noncommital readings as "nonspecific infiltration," "basal infiltrate," and others.

It is the purpose of this presentation to review the roentgenographic features of pulmonary artery occlusion as described in the literature and as recognized in a series of cases in this hospital.

The radiographic signs of pulmonary artery occlusion comprise changes in the pleural shadows, in the pulmonary parenchymal shadows, in the shadows of the lung vessels, in the cardiac contours, and in the position of the diaphragm. The following outline of topics has been used in an attempt at an organized presentation:

The chest film shows:

1. No demonstrable abnormality.
2. Pleural effusion or reaction as the only sign.
3. Focal parenchymal density, with or without pleural reaction.
4. Pneumothorax.
5. Changes in the peripheral vascular shadows.
6. Changes in the cardiac contours.
7. Elevation of the diaphragm.

The distinction between pulmonary artery occlusion without infarction and occlusion with infarction is emphasized.

When there is occlusion of a pulmo-

nary artery, the chest film shows one of the following:

1. NO CHANGE. This is by far the most frequent occurrence. It is impossible to obtain an adequate statistical idea of the frequency of pulmonary emboli which are silent, that is, emboli which have no manifestation, either clinically or on the chest film, but it is suggested that a great majority of pulmonary vascular occlusions are of this nature. In order for pulmonary artery occlusion to be evident on a chest film, the occlusion must involve a fairly large vessel, or there must be a sufficient number of small emboli to cause significant functional impairment of flow through the pulmonary vascular bed. If neither of these obtains, then, for identification on the chest film, there must be an infarct, (necrosis of lung tissue) causing one or more localized parenchymal densities, which are usually associated with the clinical symptoms of chest pain (pleuritic in nature) and, frequently, of fever and hemoptysis.

2. PLEURAL REACTION OR EFFUSION AS THE ONLY ROENTGENOGRAPHIC SIGN (Moberg[10]). When pleural reaction occurs as the result of pulmonary artery occlusion, it always indicates that infarction has occurred, although the area of infarction frequently may be hidden by the pleural density. A pulmonary infarct always extends to the pleural surface, where it gives rise to a fibrinous exudate overlying the infarcted area. The reason for the extension to the pleural surface is the fact that the portion of the lung distal to the occlusion becomes necrotic, there being relatively little collateral circulation from the surrounding pulmonary artery bed. Where there is embolism alone and no death of lung tissue, no pleural reaction and, hence, no effusion occur. Although pleural reaction secondary to pulmonary infarction is nearly always accompanied by some pleuritic pain, the degree of effusion may be sufficient to prevent the rubbing together of the inflamed pleural surfaces. Hence some patients may not complain of such pain.

A rare manifestation of pulmonary infarction is the development of empyema or infected pleural effusion.

3. FOCAL PARENCHYMAL DENSITY (ONE OR MORE), WITH OR WITHOUT PLEURAL REACTION. (Kirklin and Faust[5]). Where there is focal parenchymal density associated with pleural reaction the pathological process is as described in the preceding section. There is infarction with secondary pleurisy. This situation is very frequent, perhaps predominant, with infarction. If there is no pleural reaction the chest film shows a density of two general types. First, the density may consist entirely of atelectasis (manifested by streaking on the film). However, the atelectasis is rarely of the lobar or segmental type. The atelectatic nature of these transient streaks in the lung fields has long been understood, as evidenced by the terms "platter atelectasis" and "discoid atelectasis." Investigation at necropsy reveals only a layer of collapsed lung to explain the density. The linear shadows are usually evanescent, as one would expect of atelectasis. Occasionally, when there is necrosis or infection in the atelectatic area, there may be persistence of the streaks. When this is noted, scarring has occurred.

The frequency of this "platter atelectasis" with pulmonary artery occlusion, and its rarity with infectious lesions of the lung make its presence very helpful in the roentgenographic diagnosis of pulmonary embolism or infarction. The streaking is generally horizontal in the lower lung fields (Figs. 1, 2), but it may be oblique or diagonal (Figs. 2, 3).

Although we know very little about the pathogenesis of these atelectatic

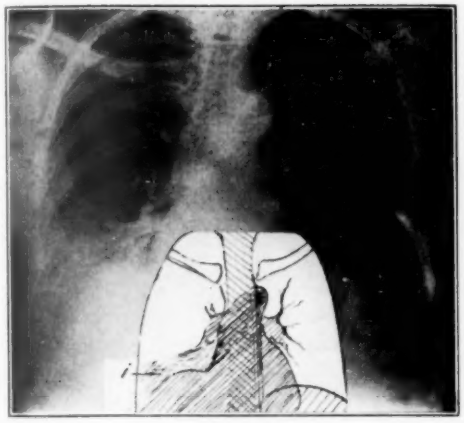


Fig. 1

Fig. 2

Fig. 1.—Forty-year-old white male with thrombophlebitis. Subsequently pleuritic pain (rt.) and hemoptysis. Atelectasis and infiltration—Right base (i).

Fig. 2.—Multiple pulmonary emboli without infarction. The linear densities represent atelectasis. No change in the vascular shadows.

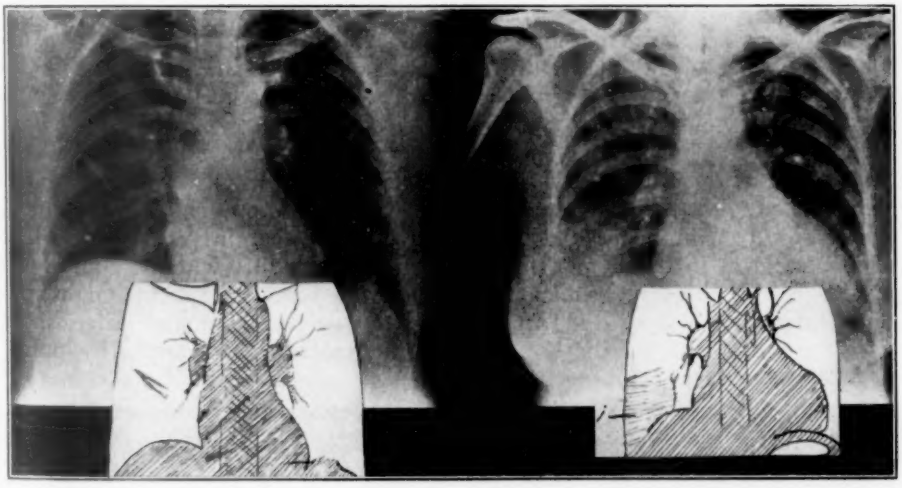


Fig. 4

Fig. 3

Fig. 3.—63-year-old white female. Transient elevation of temperature and a little cough after Cholecystectomy. Streak of oblique atelectasis—RLL.

Fig. 4.—56-year-old colored female. There was marked aortic stenosis with a large RLL infarct at necropsy.

streaks (Fleischner, Hampton and Casthman[1]), we believe that their general course and appearance are determined by the more rigid bronchial and vascular structures in the area of collapse. These linear shadows are frequently seen in postoperative chest films, and, although they are termed, noncommittally, "postoperative atelectasis," we are inclined to believe that the great majority are due to pulmonary emboli. It must be admitted, however, that subphrenic inflammation may cause basal atelectatic streaking indistinguishable from that associated with pulmonary embolism. Why pulmonary embolization should result in focal atelectasis is an unanswered question. Functionally it would appear that focal atelectasis in the lung corresponds to a localized pulmonary "shut-down," something possibly analogous to areas of focal vascular shut-down in the kidney. Where this occurs there seems to be evidence that the bronchial artery circulation "takes over" and may actually be increased*. While it has been shown experimentally that embolization of the pulmonary artery results in bronchospasm (Jesser and de Takats[4]), bronchospasm alone would not be sufficient to account for the atelectasis. Occlusion of a bronchus below the segmental level in the human lung is by itself probably not sufficient to cause atelectasis, since the area of lung deprived of air by the bronchial occlusion is evidently aerated from the surrounding lung tissue.

These linear atelectatic streaks may simply disappear, or they may be followed by definite parenchymal consolidation. Where there is consolidation, infarction has occurred and roentgenographic changes are usually well developed by the time the patient has clinical symptoms. Consolidation densities, as opposed to atelectatic streaks, never result from embolism without infarction. It seems likely, on the basis of a review of a number of cases of pulmonary infarction, that consolidation probably supervenes within a matter of 3 or 4 hours, once actual infarction has occurred. The consolidation is caused by hemorrhage into the alveoli of the infarcted area. This hemorrhage eventually organizes and sometimes leaves a horizontal or linear scar as the only parenchymal residue (Fig. 12). While it is hard to obtain an accurate knowledge of the pathologic physiology of early pulmonary infarction, it seems that infarction may occur at any time in an embolized area. In general, infarction in an embolized area of lung is the result of inadequate circulation from the bronchial arterial system. This idea forms the basis for the teaching that pulmonary infarction can only occur in the presence of congestive heart failure with elevation of the venous pressure and relative failure of the bronchial circulation. While it is certainly true that the great majority of infarcts occur in patients suffering from congestive heart failure (Fig. 4), it is equally true that infarction occurs not infrequently in postoperative patients or in patients who have thrombophlebitis without clinical evidence of heart failure. One might speculate that the pulmonary arteriospasm and bronchospasm caused by pulmonary embolism may sometimes be associated with corresponding spasm of the bronchial artery of a degree sufficient to allow necrosis of the lung.

The localization of the focal densities associated with pulmonary artery occlusion is of considerable interest. Atelectatic changes (linear streaks) are usually noted at the bases, although they may occur in the upper and mid

*Unpublished observations on incidental findings in angiocardiography.

lung fields as well. When they are found in the upper lung field they tend to be more oblique, radiating upward and outward from the hilar areas on the PA projection. When the lesion is a frank *infarct*, it is more commonly localized in the right lower lobe. A review of over 100 cases of necropsy-proven pulmonary infarction reveals localization in the right lower lobe in 70% of the cases. Investigation of the localization of emboli in the same series shows no such selectivity, there being a more-or-less random distribution. Thus the right lower lobe localization appears to be well established, although the mechanism of it is not.

The morphology of the pulmonary densities is varied. They may be single or multiple. It is important to emphasize that only about 10% of the pulmonary infarcts have the characteristic wedge-shape described so frequently. When the so-called wedge density is seen, however, it is of great diagnostic importance. Here again, the peripheral localization of the density is helpful in establishing the diagnosis (Figs. 7, 9). If a pulmonary lesion is central and on no projection extends to the pleural surfaces, it is not a pulmonary infarct.

The following paragraphs outline the usual parenchymal radiographic patterns pulmonary infarction may take:

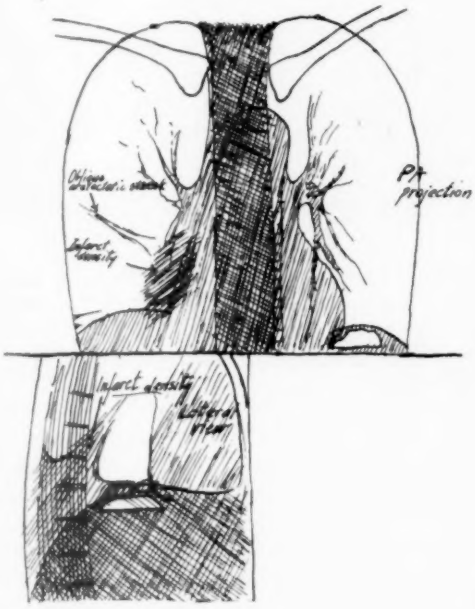


Fig. 5

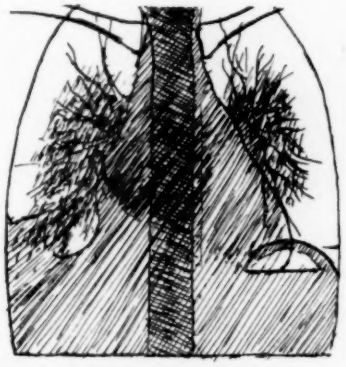


Fig. 6

Fig. 5.—"Pneumonitis type. Single infarct—right lower lobe. Density obliterates diaphragm posteriorly on lateral view—a very frequent form. There were probably several emboli. Note the atelectatic streaks in the right costo-phrenic angle.

Fig. 6.—"Edema" type. Single infarct—right lower lobe. "Edema" type. Forty-six-year-old white male with severe rheumatic mitral-valve disease. On the original film the infiltrate was confluent with the central pulmonary edema, and was not diagnosed. The infarct might have been suspected, though, because it is unusual for pulmonary edema to involve the extreme costo-phrenic angles. There were other smaller infarcts at necropsy six days later.

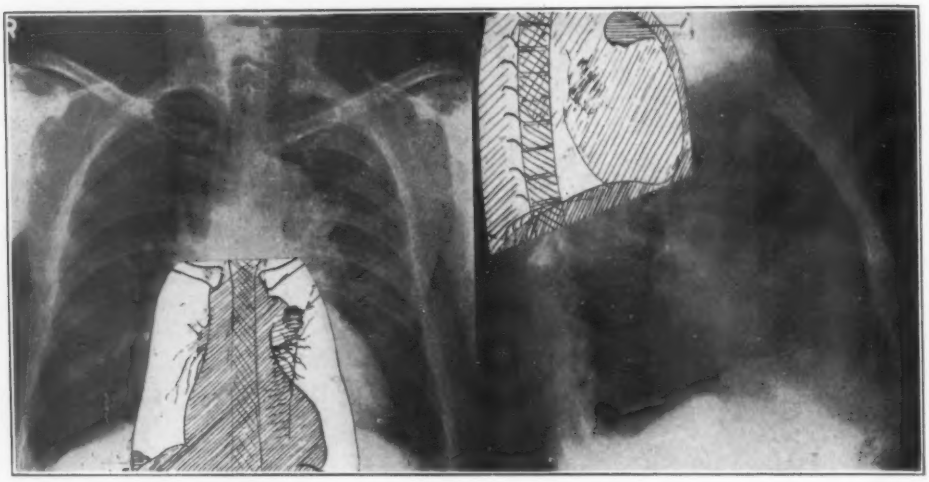


Fig. 7 Fig. 8

Fig. 7.—Forty-two years old cardiac with bilateral pleurisy, hemoptysis and fever. Indistinct infarct density adjacent aortic arch (left) and well defined density nestling in right costophrenic angle (i).

Fig. 8.—Same patient. Lateral projection. Complete clearing of tumor-like infarct shadow (i) two months later.

Fig. 9.—"Wedge" type. Single infarct—left upper lobe. Sixty-five-year-old white male. Sudden onset of left pleuritic pain four days after radical perineal prostatectomy. Clinical proof only. The wedge shape is typical, but rare.

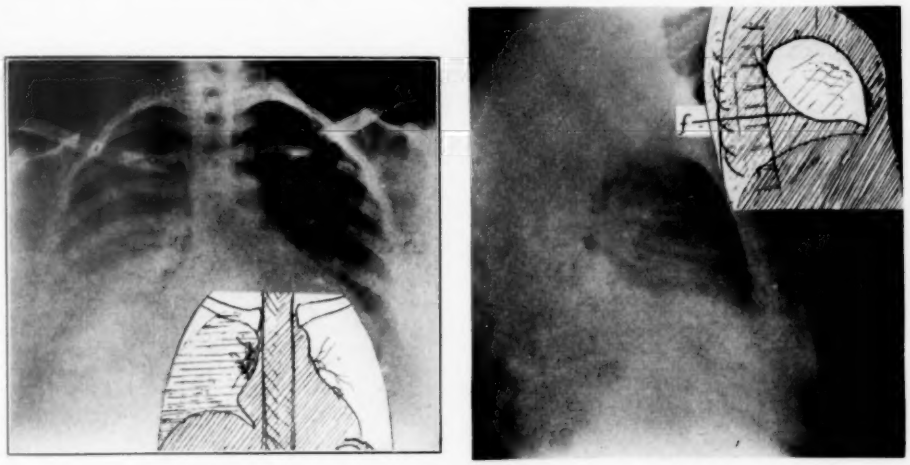
(a) *"Vague infiltrate," or "pneumonitis" type.* The most frequent roentgenographic manifestation of a pulmonary infarct is a vaguely defined but fairly well localized opacification in the right lower lung field (Figs. 1, 5). More often than not the lesion is associated with some degree of atelectatic streaking or loss of volume and there may be associated pleural reaction. In cardiac patients a pulmonary parenchymal lesion extending to the pleural surface suggests the possibility of pulmonary infarction above all other lesions (Fig. 6).

(b) *"Nestler."* An additional morphologic form of pulmonary infarct which is almost as typical as the so-called wedge form and which is much more frequent statistically is a type consisting of a density nestling in the costophrenic angle with a convex upper border (Fig. 7). In a postoperative patient who suddenly experiences chest pain, the finding of a density of this type is pathognomonic of pulmonary infarct.

(c) *"Wedge Density."* The shadow of a wedge with its base against the

pleural surface is a rare, though diagnostic picture (Fig. 9; also Fig. 8).

(d) *"Lobar Pneumonia Type."* Another morphologic form of pulmonary infarct seen fairly frequently is the so-called "pneumonia" type, which simulates lobar pneumonia (Fig. 10). In such cases there is usually heart failure, often with massive hemoptysis. In other cases of less extensive involvement the lesion may simulate bronchopneumonia or atypical pneumonia, but, again, the association of considerable atelectasis with the density is a



a *b*

Fig. 10*a*.—30-year-old colored male with sickle-cell anemia. Massive infarct—RLL. (Necropsy proof.)

Fig. 10*b*.—Same case— lateral projection. f—Shadow of right oblique fissure with consolidated, partially atelectatic RLL behind. (f—oblique fissure.)

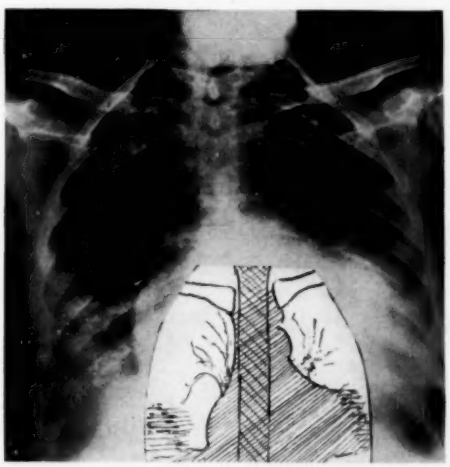


Fig. 11.—46-year-old-colored male. Myocarditis of unknown etiology with multiple pulmonary infarcts (necropsy proof). With such marked cardiomegaly the infarcts could be taken for pulmonary edema.

sign pointing toward pulmonary infarction.

(e) *"Tumor Type."* A fifth rather rare yet striking morphologic form of pulmonary infarct might be termed the "tumor" type (Figs. 7, 8). In some instances this is a modified "wedge" type. Here there is a well-defined subplural mass having the shape of a mound or cone with its base against the pleural surface. Perhaps the "nestler" associated with a density filling the costophrenic angle might be also considered a variant of this. It should be noted, however, that neoplasms seldom if ever present in the costophrenic angle, so it would seem advisable to keep the "nestler" in a separate morphologic category.

(f) *"Edema Type."* Another important type of density caused by pulmonary infarction is that simulating pulmonary edema. This is of considerable clinical importance because of the frequency of pulmonary infarction in congestive heart failure (Fig. 6, 11). Small infarcts in cardiac patients may be completely hidden by pulmonary edema or congestion, and a large area of infarction may simulate an area of pulmonary edema. Once again, linear atelectasis is an important diagnostic clue.

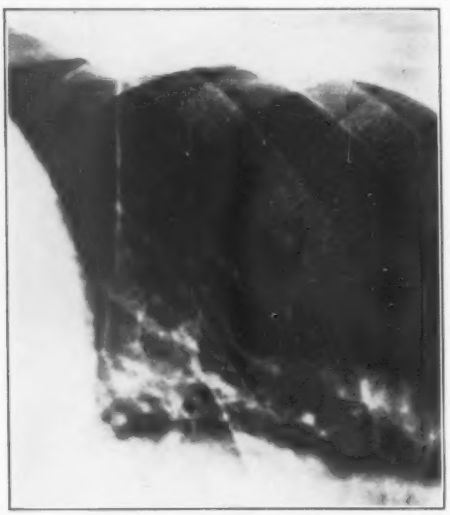


Fig. 12

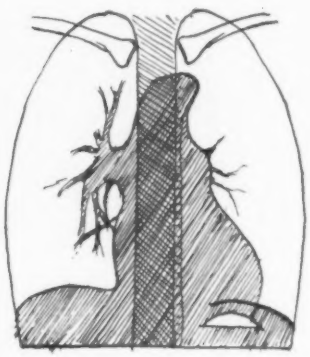


Fig. 13

Fig. 12.—Horizontal scar resulting from pulmonary infarction several years before. (Same case as Fig. 1.)

Fig. 13.—Massive pulmonary embolus, left. Blanching of peripheral vessel shadows, left. Vessels accentuated on the right. Prominent main pulmonary artery.

When an infarct heals it may disappear without visible residue, or it may leave a linear or streaky atelectatic scar (Fig. 12).

4. PNEUMOTHORAX. This is seen as a rare manifestation of pulmonary infarct (Marks[9]), and was not encountered, as a proven instance, in the present series.

Special mention should be made of the rarity of pulmonary infarction in children. It seems that some form of

blood dyscrasia or some septic phenomenon is a prerequisite for infarction of the lung in young children. In this series, pulmonary infarcts in children are generally associated with leukemia, bacterial endocarditis or sickle-cell anemia (Figs. 10*a*, 10*b*). All patients who have sickle-cell anemia seem prone to the development of pulmonary infarction. Indeed, it appears that the predilection of sickle-cell-anemia patients for pneumonia-proneness may quite possibly be the result of misdiagnosed pulmonary infarction. It is suspected that this is also true of patients with congenital cardiac lesions and polycythemia. Septic emboli from various sources often present a complicated roentgenographic picture. Common to a great many of these lesions is the underlying element of streaking or linear density corresponding to atelectasis. When the lesions are multiple, the diagnosis is easier, however.

5. CHANGES IN THE PERIPHERAL VASCULAR SHADOWS. Changes in the peripheral vascular shadows frequently are an accompaniment of pulmonary embolism, with or without pulmonary infarction (Lodge[7], Shapiro and Rigler[12], Westermark[13]). However, changes of this nature are seldom recognized in many cases of pulmonary embolism. Spasm of small pulmonary arteries probably has no roentgenographic manifestation that can be identified with routine techniques. Only when this spasm is accompanied by atelectasis do we have roentgenographic evidence of the process. As a rule, embolism must involve a large vessel, probably a lobar vessel or larger, in order to cause roentgenographically demonstrable changes in vessel caliber. Then, the changes are more often an over-all blanching of the peripheral lung field in the involved area than a measurable decrease in the caliber of a given vessel (Figs. 13, 14). This generalization is necessitated by the difficulty involved in measuring the caliber of individual vessels (Lodge[7]). It is quite possible that tomographic examination of individual vessels will make possible more precise evaluation of pulmonary artery caliber (Hornykiewytsch and Stender[3]). Selective angiography of the pulmonary arteries offers promise here, also, though the procedure is admittedly too rigorous for routine use (Lohr, Scholtze and Grill[8], Nordenstrom[11]). Immediately after pulmonary embolism there may be either no change in the caliber of the vessels or these may be narrowed (Figs. 13, 14). The reason for the reduction in caliber must be arterial spasm and elastic contraction. Arteries which still contain blood, and, which are not in spasm or passive collapse, will present precisely the same roent-

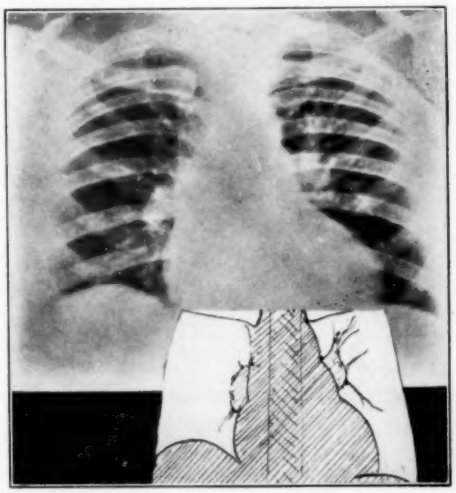


Fig. 14.—Thirty-eight-year-old colored male admitted because of progressive dyspnea. At necropsy there was total embolic occlusion of the rt. pulmonary artery. There were several emboli on the left. Note "blanching of rt. lung.

genographic pictures as when not occluded.

Following this initial period of variability, which may last several days to several weeks, the normal-sized vessels may become smaller (Fig. 14) due to organization of the clotted intraluminal blood and its fibrotic contraction, or they may continue to be of normal caliber because of recanalization. The narrowed vessels may return immediately to normal caliber, because of cessation of vasospasm and recanalization, or they may remain narrowed and become actually thinner, because of organization of the thrombus, with eventual fibrotic obliteration.

A related process, but one with considerably different clinical manifestations (and one which is difficult to diagnose both clinically and radiographically), is that of multiple small pulmonary emboli. Here the patient usually presents with the complaint of gradually increasing dyspnea and, possibly, with congestive heart failure. The cardiac contours are often abnormal (Fig. 15), but the peripheral lung fields may show no evidence of the extensive embolization has occurred by the time the patient presents with symptoms. Still, it is usually possible to infer from the chest film that there is some disturbance of the pulmonary vascular tree. Patients presenting with dyspnea and congestive heart failure alone show accentuation of the pulmonary vascular markings, with enlargement and blurring of the vessel shadows far out into the periphery of the lung fields. In cases of extensive small multiple pulmonary emboli, however, the peripheral lung fields are usually avascular in appearance, even though the hilar portions of the pulmonary arteries are large (Fig. 15). This finding of blanched peripheral lung fields with abnormalities of the cardiac contours is extremely helpful in making the diagnosis. There is usually no sign of

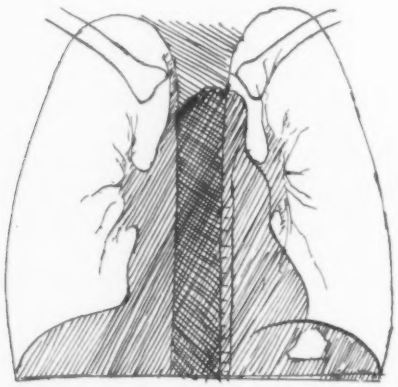


Fig. 15

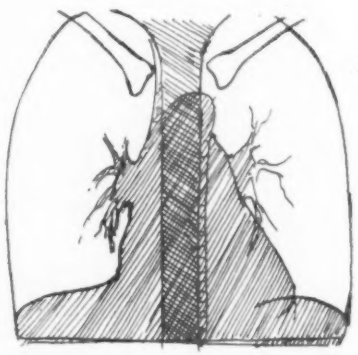


Fig. 16

Fig. 15.—Chronic cor pulmonale due to repeated bouts of small emboli to the lungs. The source was not identified—even at necropsy.

Fig. 16.—Acute cor pulmonale, secondary to several large emboli to both lungs. Peripheral vessels somewhat less prominent than normal. Straightening of the left heart border and moderate enlargement of the heart shadow (acute right ventricular dilatation). No infarction or atelectasis.

atelectasis or of pulmonary infarction in this syndrome.

6. CHANGES IN CARDIAC CONTOUR. Changes in the cardiac contour are those of acute and chronic cor pulmonale. This is quite apart from the cases in which the primary difficulty is cardiac and pulmonary embolism or pulmonary artery thrombosis has occurred secondary to congestive heart failure. In such cases as the latter it is extremely difficult or impossible to recognize cardiac changes secondary to the added burden on the right heart. In acute cor pulmonale there is usually rather nondescript widening of the cardiac silhouette, with particular prominence of the right heart border corresponding to the contour of a dilated right atrium. Also, there may be some degree of straightening of the left heart border caused by moderate dilatation of the outflow tract of the right ventricle and pulmonary artery (Fig. 16). It is the rule, however, that the electrocardiographic findings are more helpful in diagnosing acute cor pulmonale than the chest film.

Immediately after massive pulmonary embolism cardiac dilatation is generally slight and, of course, there has been no opportunity for hypertrophy to develop (*acute* cor pulmonale). The compensatory cardiac changes of *chronic* cor pulmonale are those of progressive hypertrophy and dilatation of the right ventricle with associated prominence of the pulmonary artery. These cause further straightening of the right heart border and further prominence of the outflow tract and pulmonary artery. Unfortunately, however, this appearance may be rather nonspecific and may give the impression of over-all cardiac enlargement (Fig. 16).

In many cases it is virtually impossible to identify the selective chamber enlargement. The left ventricle is rotated posteriorly, and the contours of the two ventricular surfaces fuse smoothly, so that no septal boundary can be identified. Particularly where there is pre-existing emphysema the heart shadow may be small, the cardiac structures being compressed and elongated by the overinflated lungs and low diaphragm respectively.

Further difficulties in the diagnosis of right ventricular enlargement and hypertrophy are due to the fact that in some cases of cor pulmonale cardiac compensation occurs through hypertrophy alone and in others chiefly by dilatation. In all cases of massive, severe pulmonary embolism, however, both elements are present in the resulting chronic cor pulmonale. Fluoroscopy is not usually of great help in the diagnosis of cor pulmonale. Where there is adequate cardiac compensation, pulsations of the right ventricle and pulmonary artery may be slightly accentuated, but they are usually normal. When the heart begins to fail, pulsations may be reduced. As a matter of fact, there may be a striking absence of pulsations in the markedly dilated hilar vessels.

7. ELEVATION OF THE DIAPHRAGM. Diaphragmatic elevation occurs frequently in pulmonary embolism alone and, even more frequently with infarction. The reason for this elevation with embolism alone is unknown. It usually involves both sides similarly, and it may be the result of reflex inhibition of inspiration because of the patient's anxiety or dyspnea. High diaphragm is not seen with a small embolism, without infarction, but only with massive embolization.

In contrast to the findings with a small uncomplicated embolus, infarction, even when small, may, and usually does, cause appreciable elevation of the diaphragm (Fig. 1), either unilaterally or bilaterally. Pleuritic pain is

the chief cause, and it results in "splinting" or "guarding" of the affected pleural surfaces by relative immobilization of the respiratory muscles.

Summary. The importance of atelectasis, especially linear, or "platter" atelectasis, in the roentgenographic diagnosis of pulmonary vascular occlusive lesions is emphasized. The various morphologic forms which a pulmonary infarct may present on the chest film are described. These include: pleural effusion, parenchymal consolidative densities resembling pneumonia, tumor, pulmonary edema, the characteristic wedge density, and densities nestling in the costophrenic angles.

REFERENCES

(1) **Fleischner, F., Hampton, A. O.,** and **Castleman, B.:** Am. J. Roentgenol., **46,** 610, 1941. (2) **Hampton, A. O.,** and **Castleman, B.:** Ibid., **43,** 305, 1940. (3) **Hornykiewytsch, T.,** and **Stender, H. S.:** Fortschr. Geb. Röntgenstrahlen, **79,** 44, 639, 704, 1953; 80, 458, 1954; **81,** 36, 134, 455, 642, 1954; **82,** 228, 331, 642, 1955. (4) **Jesser, J. H.,** and **deTakats, G.:** Surgery, **12,** 541, 1942. (5) **Kirklin, B. R.,** and **Faust, L. S.:** Am. J. Roentgenol., **23,** 265, 1930. (6) **Levy, H.:** Ibid., **35,** 635, 1936. (7) **Lodge, T.:** Brit. J. Radiol., **19,** 1, 77, 1946. (8) **Löhr, H., Scholtze, H.,** and **Grill, W.:** Acta radiol., **51,** 33, 1959. (9) **Marks, J. H.:** New England J. Med., **223,** 934, 1940. (10) **Moberg, G.:** Acta radiol., **29,** 7, 1948. (11) **Nordenstrom, B.:** Ibid., Supplement 108, 1, 1954. (12) **Shapiro, R.,** and **Rigler, L. G.:** Am. J. Roentgenol., **60,** 460, 1948. (13) **Westermark, N.:** Acta radiol., **19,** 357, 1938.

PROCEEDINGS OF

The Physiological Society of Philadelphia

SESSION OF FEBRUARY 17, 1959

SEMINAR ON ADRENAL CORTICOSTEROIDS

Certain Defects in the Biosynthesis of Steroids in Man. A. M. BONGIOVANNI, M.D. (Department of Pediatrics, University of Pennsylvania Medical School). Evidence is presented that in the normotensive form of the adrenogenital syndrome, there is primarily a lack of the 21-hydroxylase in the diseased gland. Patients with this disorder regularly excrete pregnanetriol in their urine, and no or very little of the expected metabolites of hydrocortisone. The large amounts of pregnanetriol suggest that there is a block in the conversion of 17-hydroxyprogesterone. Detailed column chromatography of the 17-ketosteroids from patients with this disorder indicates that there are relatively large amounts of 11-hydroxylated compounds. Thus, in this form of the disorder, the 11-hydroxylase is present. Furthermore, direct studies, employing normal human adrenal glands and two glands from patients with the disease, with 17-hydroxyprogesterone as a substrate, reveal the ability of the former to convert the substrate to hydrocortisone, whereas the latter was unable to do so.

Studies of patients with the hypertensive form of the disorder have large amounts of Porter-Silber chromogens in both their blood and urine. The steroid reacting with this reagent proved to be not hydrocortisone, but deoxycortisol (Substance S). In addition, large amounts of the completely reduced metabolite of deoxycorticosterone was present in the urine, suggesting that deoxycorticosterone itself was the cause of hypertension. Detailed column chromatography of the 17-ketosteroids from a patient with this form of the disease revealed that the large quantities of such compounds consisted almost entirely of etiocholanolone, and there was no 11-hydroxylated 17-ketosteroids. Therefore, there is a lack of 11-hydroxylase in this type of the disease, and the presence of 21-hydroxylase is indicated by these results. Thus, there is a difference in the enzymatic defect in the two forms of the disease, although in both virilization is a common feature.

The studies indicating the blocks in biosynthesis of hydrocortisone in this disorder of man point to a pathway for such biosynthesis in man, which is probably identical with that described for beef in the perfusion studies of Hechter.

The Production of 20-Alpha and 20-Beta Reduced Hydrocortisones by Human Adrenal Incubates and Their Relationship to Hypertension. JOSEPH C. TOUCHSTONE, PH.D., AND D. Y. COOPER, M.D. (Harrison Department of Surgical Research, School of Medicine, University of Pennsylvania). Toluene: propylene glycol paper chromatograms of extracts of incubated adrenal tissue slices have invariably shown zones which absorbed ultraviolet light at 245 mμ which were more polar than hydrocortisone. Elution of these zones and rechromatography in the system chloroform: formamide re-

sulted in the separation of four well defined spots absorbing ultraviolet light at 245 mμ. The two least polar of these four substances have been identified as Δ^4-pregnene-11β-17α-20α-21-tetrol-3-one and its 20β-epimer by characteristic mobilities in paper chromatograms as the free alcohol and as their acetates. These gave no reaction with blue tetrazolium. On oxidation with sodium bismuthate, both substances gave Δ^4-androstene-11β-ol-3, 17-dione. The absorption spectrum in sulfuric acid of these substances and their oxidation products were identical with the spectrum shown by the reference steroids. The identifications were substantiated by infrared spectrometry performed by courtesy of Dr. T. F. Gallagher. The production of the 20α-epimer was 33 μg. per gram of incubated tissue, while that of the 20β-epimer was 36 μg. per gram. The addition of corticotropin to the incubation medium caused a 100% increase in the production of these metabolites. Preliminary calculations indicate that with an increase in the blood pressure of the patient from whom the adrenal was removed there was an increased production of the 20 reduced hydrocortisones. This is different from the negative correlation we have previously reported for production of hydrocortisone by the same incubates.

Enzymatic Reduction of Steroid Aldehydes. JOHN J. SCHNEIDER, M.D., PH.D., (Department of Medicine, Jefferson Medical College). Following the observation that cortisone-21-aldehyde rapidly is reduced to cortisone in the presence of a soluble enzyme from rat liver and dihydrodiphosphopyridine nucleotide (J. Am. Chem. Soc., **75**, 2024, 1953) a more detailed study of this reaction has been made.

The enzyme is stable at 50° at neutral pH, is precipitated by ammonium sulfate at 0.4 to 0.55 saturation and retains its activity following dialysis and lyophilization. In addition to reducing the above aldehyde, it can reduce the aldehyde group of $\Delta^{1,4}$-pregnadiene-17α-ol-21-al-3,11,20-trione and of 3-ketobisnor-4-cholene-22-al. The triterpene gummosogenin and the adrenal hormone aldosterone were unaffected. These reductions also were catalyzed by crystalline liver alcohol dehydrogenase and to a minor extent by crystalline yeast alcohol dehydrogenase under the above conditions.

All attempts to demonstrate the formation of the steroid aldehyde by incubating the corresponding alcohol with the above enzymes plus diphosphopyridine nucleotide at a pH in the range 8 to 9 have failed.

BOOK REVIEWS AND NOTICES

LABORATORY APPLICATIONS IN CLINICAL PEDIATRICS. By IRVING J. WOLMAN, M.D. Pp. 1019. New York: McGraw-Hill Book Co., Inc., 1957. Price, $15.00.

THE author has undertaken the monumental task of writing a textbook of laboratory methods and their application to clinical problems in pediatrics. The scope of this volume may be evident from a listing of the major sections: Red Cells and Hemoglobin; Blood Grouping; Transfusions, and Erythroblastosis; Leukocytes; Blood Clotting and Hemorrhagic Disorders; Spleen; Bone Marrow; Urine and Urine Analysis; The Kidney and Its Diseases; Cerebrospinal Fluid; The Liver and Its Diseases; Blood Chemistry: Organic and Inorganic Constituents; Vitamins; Gastrointestinal Tract; Endocrine System; Infectious Diseases; Chemotherapy; and Obscure Diseases and Poisonings.

This volume reflects the extensive experience of the author. It would be of value especially to general physicians whose practice includes the clinical care of infants and children. C.Z.

THE KIDNEY: AN OUTLINE OF NORMAL AND ABNORMAL STRUCTURE AND FUNCTION. By H. E. DE WARDENER, M.D., St. Thomas's Hospital, London. Pp. 338; 74 ills. Boston: Little, Brown and Company, 1958. Price, $10.00.

THIS compact book is an outline of renal function and structure of the normal and diseased kidney, written in a style for easy reading and should be very useful to the student as well as the practitioner who does not specialize in renal disease.

The book contains a concise description and discussion of methods employed for determining kidney function and many valuable practical points suggesting the author's intimate clinical experience with tests of renal function.

In addition to the four main syndromes which occur in renal disease, the section discussing the relationship between disturbances of renal function and electrolyte disorders is handled in an informative manner.

The latter part of the book has short clinical chapters devoted to specific renal diseases and to generalized diseases which manifest renal abnormalities. These chapters will be helpful as a quick and up-to-date reference. I.G.

A DOCTOR SPEAKS HIS MIND. By ROGER I. LEE, M.D. Pp. 120; 1 ill. Boston: Little, Brown & Co., 1958. Price, $3.00.

THE author well describes his book as "musings, mostly mundane, but related to medical matters, especially concerned with a changing medical profession attempting to accommodate itself to a changing society and to scientific advances. The musings are mostly mild, but at times militant in defense of the medical profession and the best care of the patient." They are also charming, well-written, entertaining, usually accurate, most of them regrettably brief, at times challenging in their vision, never pedantic. They even lend themselves to being read aloud (try "Crusades" first). Laymen as well as physicians will enjoy this new book by the author of "The Happy Life of a Doctor." R.K.

THE HEALING OF WOUNDS. Edited by MARTIN B. WILLIAMSON, PH.D., Professor of Biochemistry, Stritch School of Medicine of Loyola University, Chicago. Pp. 202; 43 ills. New York: McGraw-Hill Book Co., 1957. Price, $7.00.

A GREAT deal of basic information about the processes involved in the healing of wounds has accumulated during recent years. In this small volume a group of outstanding investigators have critically appraised much of the work in this area. Included are discussions of the Metabolism of Proteins and Amino Acids during Wound Healing, the Role of Ground Substance, Vitamin C, and Collagen in Wound Healing, and of the Hormonal Influences in Granulation Tissue Formation.

Clinicians, biochemists, histologists and others interested in the phenomena associated with wound healing will find this an extremely interesting and valuable book. C.Z.

ETIOLOGY AND TREATMENT OF LEUKEMIA. Edited by WALTER J. BURDETTE, PH.D., M.D., F.A.C.S., Professor and Head of the Department of Surgery, University of Utah College of Medicine. Pp. 167; 14 ills. St. Louis: C. V. Mosby Co., 1958. Price, $4.00.

THE Proceedings of the First Louisiana Cancer Conference are recorded in this volume. The presentations are all of unusually

high quality and include discussions of Viruses and Cancer (by J. T. Syverton), the Etiology of Leukemia (by the late Arthur Kirschbaum), the Infectious Concept of Leukemia (by L. Gross), and the Diagnosis of Leukemia (by C. S. Sprague). Leukemia therapy is discussed by several workers well-known in the field, namely, A. Gellhorn, J. V. Schlosser, Morwenna Till, J. Burchenal, and W. R. Arrowsmith. Finally, there is an excellent summary appraisal of current knowledge regarding the etiology and treatment of leukemia.

This volume is recommended to all who are interested in the leukemia problem.

C.Z.

HORMONE PRODUCTION IN ENDOCRINE TUMOURS, VOL. 12, COLLOQUIA ON ENDOCRINOLOGY. Edited by G. E. W. WOLSTENHOLME, O.B.E., M.A., M.B., B.Ch., AND MAEVE O'CONNOR, B.A. Pp. 351; 60 ills. Boston: Little, Brown and Co., 1958. Price, $9.00.

THE latest of this important and interesting series of Symposia concerns itself with hormone production in various endocrine tumors. The hormonal aspects of pituitary, thyroid, adrenal, ovarian, testicular, and islet cell tumors are considered. Much recent biochemical information is correlated with the older physiologic and pathologic knowledge. The presentations are all authoritative and their value is further enhanced by the inclusion of the general discussion which followed each paper.

In addition to the usual index for the material included in this volume, there is appended a comprehensive index for Vols. 1 through 12. Endocrinologists, biochemists, and others interested in laboratory and clinical problems associated with functional tumors will find much of value in this volume.

C.Z.

ON THE UTILITY OF MEDICAL HISTORY. Monograph 1. Institute on Social and Historical Medicine. Edited by IAGO GALDSTON, M.D. Pp. 73. New York: International Universities Press, Inc., 1957. Price, $2.00.

THIS is the first of a series of monographs devoted to the proceedings of the Institute on Social and Historical Medicine, held at the New York Academy of Medicine. It contains six lectures whose titles are informative and significant: On the Utility of Medical History; Purposes and Values of Medical History; A Critique of Medical History; Psychology and Medical History; On the Teaching of Medical History; and Historians, Imperialists and Prophets. Two are by Professors of Medical History, one, by a Professor of Philosophy, one by a Professor of Health Education and two authors are respectively the Executive Secretary of the Committee on Information and Chairman of the Section on Historical and Cultural Information of the New York Academy of Medicine. Lack of space restricts the reviewer to cite only those few significant thoughts in the text: when properly presented medical history counterbalances the effects of specialization and helps the medical man to synthesize for himself an organic conception of medicine. The history of medicine can lay bare the origins of medical ideals and values and explain their role and significance. Disquieting but irrefutable is the thought that in this country the language barrier makes access to other than English literature difficult and that, concomitant with the loss of Latin and Greek the familiarity with older periods has also suffered: these are some of the factors which are tending to transform the doctor into a diagnostic and therapeutic technician. Better proofreading should have protected one writer against his misspelling of "syphilis."

R.K.

DOCTOR AND PATIENT IN SOVIET RUSSIA. BY MARK G. FIELD. Pp. 266. Cambridge, Mass.: Harvard University Press, 1957. Price, $5.00.

THIS is a study in the sociology of the medical profession in Russia, not an assessment of Soviet medicine or its techniques. It is based upon a varied source material: interviews with over 1600 former Soviet citizens, lay and medical, at the time displaced in Munich, Germany, or in New York City; a discerning study of Soviet publications; and a 4-week visit in Russia, a third of the time as a member of an American medical mission in 1956. The work was done under the aegis of the Russian Research Center of Harvard University. Part 1 deals with the organization of medical service, first in Tsarist Russia, then its development under the Soviets. Part 2, on the physician, takes up the medical profession and its transformation into an employee group (sharply down-graded, so that it is comparable both in low prestige as well as salary to primary school teachers in the United States; overwhelmingly limited to women as a stop-gap before marriage and an added side source of income after marriage); the recruitment of medical personnel and its allocation; the prerequisites for medical practice (remuneration, facilities and in-

strumentation); cooperation of medical and ancillary personnel, and the manner of dispensing of professional services; and the dilemma in which the physician constantly finds himself between his responsibility to the State and the care of the patients whose excused absence from work depends upon medical certification of illness, frequently feigned. Part 3 considers the viewpoint of the patient: the brand of medicine disposed at different social levels: officials, secret police, intelligensia, several grades of workers, collective farmers; the availability and competence of physicians in relation to patients and their social levels, and rapport between physician and patient. There are some interesting data on the reactions of displaced Russians to German socialized medicine, largely favorable, and to American medicine, largely unfavorable. This book is a valuable contribution to historical, medical and social literature that deserves careful reading not only by physicians but legislators and all who are concerned with any phase of the social aspects of medical care. R.K.

READINGS IN MEDICAL CARE. Edited by the Committee on Medical Care Teaching of the Association of Teachers of Preventive Medicine. Foreword by GEORGE PACKER BERRY, M.D., Dean, Harvard Medical School. Pp. 708; 33 ills. Chapel Hill: The University of North Carolina Press, 1958. Price, $6.50.

AN anthology of selected writings on problems of medical care in the United States, this volume gathers together many and varied documents on topics of public health importance. Compiled during the past decade by the Committee on Medical Care Teaching of the Association of Teachers of Preventive Medicine, these publications, studies dating back to the 1920's as well as more recent papers, provide a broad base for an understanding of current problems in providing adequate, comprehensive medical care for all. Previously scattered in numerous technical books, journals and monographs, these reports, culled by a group of experts, offer representative selections from a wide field of health interests.

Thirteen chapters focus on challenging problems facing the health professions today and tomorrow: Problems in Medical Care, General Background; The National Health Picture; Adequacy of Medical Care; Costs of Medical Care; The Medical Care Team; Hospitals; Coordination in Health and Medical Service; Care of Long-Term Illness; Rural Medical Care; Public Medical Care; Medical Care in Industry; Medical Care Insurance; Principles and Proposals. Adequate footnotes and an index are appended to the text.

In his *Foreword* to this valuable book, Dean Berry writes: "By 1980—less than 25 years from now—it is reliably estimated that the population of the United States will have grown from 173 to 240 million. Medicine must prepare at once for the largest increase in population in our history. . . . The upgrading of our people in terms of education, occupation, and income betokens increased demands for medical services. *Indeed, many of our people now regard the opportunity for good health as their basic human right.* . . . It is implicit that the physician as a citizen must bring to bear on social problems his special education, proficiency, and responsibility. He is expected to advise his community, his state, his nation—expected to play a role of leadership as our democratic society endeavors to extend the benefits of expanding scientific knowledge to the service of mankind." F.R.

ANNUAL REVIEW OF BIOCHEMISTRY, Vol. 26, 1957. Edited by J. MURRAY LUCK, FRANK W. ALLEN AND GORDON MACKINNEY. Pp. 768; illustrated. Palo Alto, Calif.: Annual Reviews, Inc., 1957. Price, $7.00.

THIS is the latest volume in this series which annually undertakes to review progress in important areas of biochemistry. Included are critical appraisals of investigations dealing with Biological Oxidations, Proteolytic Enzymes, Lipide Metabolism, Carbohydrate Metabolism, Water Soluble Vitamins, Fat Soluble Vitamins, Nutrition, Chemistry of Proteins, Amino Acid Metabolism, and Chemistry of Carbohydrates.

Other chapters assess the recently reported work on Nucleic Acids, the Biochemistry of Steroid Hormones, Haem Pigments and Porphyrins, and the Biochemistry of Muscle. Of especial interest are the sections on "Biochemistry in the U.S.S.R.," and "Clinical Applications of Biochemistry," as well as the splendid prefatory chapter in which Sir Rudolph Peters writes a personal review of "Forty-Five Years of Biochemistry."

All workers in biochemistry and related disciplines will find this volume to be as useful and invaluable as its predecessors. C.Z.

ESSENTIALS OF GYNECOLOGY. By E. STEWART TAYLOR, M.D., Professor and Head of the

Department of Obstetrics and Gynecology, University of Colorado School of Medicine. Pp. 502; 343 ills., 4 in color. Philadelphia: Lea & Febiger, 1958. Price, $12.00.

At first examinations Taylor's "Essentials of Gynecology" appears to be quite similar to other textbooks already available, but as one studies it certain differences become obvious. It has been prepared for the use of medical students and family physicians and as a consequence is somewhat less inconclusive than some texts. The common gynecologic conditions are discussed in enough detail to cover each completely and basic information concerning the less frequently encountered lesions is included. The diagnostic and therapeutic procedures discussed are, for the most part, those which can be carried out without complicated equipment or large laboratories, and an attempt has been made to emphasize studies which can be performed in the physician's own office.

In addition to discussions of the disease processes which affect the various portions of the genital organs there are excellent chapters on the influence of the adrenal, pituitary and thyroid glands on genital function and another on pediatric gynecology. The text is well written, complete and interesting but there are numerous typographical errors such as "pyrometrium" and pruritus is consistently called "pruritis." The material is well illustrated with cuts, black and white prints and photomicrographs; unfortunately many of the latter are not clearly reproduced.

Although this is basically an excellent text, there are several improvements which might be considered for subsequent editions to make it more valuable for relatively inexperienced physicians. In many instances either the recommendation of a drug or the dosage is indefinite. The author often avoids using familiar names for indications ". . . 0.625 to 1.25 mg. of one of the oral natural or synthetic estrogens every day for three weeks . . ." He also uses terms such as "appropriate antibiotic therapy," and others. Another serious omission is what appears to be a studied attempt to avoid mentioning emotional problems such as frigidity, dyspareunia and premenstrual tension. No mention is made of psychogenic causes of pruritus, infertility and other conditions. Operations for fistulas, pelvic relaxations, uterine cancer, tubal obstruction and benign uterine tumors are described in considerable detail but I was unable to find a description of the technique for diagnostic curettage which certainly is a procedure which family physicians should be able to perform. J.W.

Soldier in White: The Life of General George Miller Sternberg. By John M. Gibson. Pp. 277; 1 ill. Durham: Duke University Press, 1958. Price, $6.75.

This is an excellent biography of General George M. Sternberg, whose career was one of the most illustrious and distinguished in the history of the United States Army Medical Service.

A pioneer bacteriologist, and later Surgeon General of the Army, he played a major role in the yellow fever research of his period. Many of his contributions to the medical literature appeared in the pages of this Journal. In addition to his specific scientific investigations, however, General Sternberg exerted a highly important and favorable influence on the progress of American military medicine.

All who are interested in medical history and in the lives of those who made significant contributions to it will find this an enjoyable book. C.Z.

Peripheral Circulation in Health and Disease. By Walter Redisch, M.D., Associate Professor of Clinical Medicine, New York University Medical College and Francisco F. Tangco, M.D., B.S., Assistant Professor of Medicine, University of the Philippines Medical School. Pp. 154; 25 ills. New York: Grune & Stratton, Inc., 1957. Price, $7.75.

This book differs in form from most others devoted to peripheral circulatory diseases. In place of discussions of pathophysiology, clinical manifestations and treatment under headings of individual disease entities, the authors have divided their work into five principal sections: 1) basic aspects of peripheral blood flow, 2) pathologic alterations in peripheral blood flow, 3) physiologic responses to disturbances in blood flow, 4) management and therapy. 5) The final section is a special study on the anatomic basis of the peripheral circulation in man based on radiographic methods including microradiographic techniques. This approach has much to recommend it but there are certain disadvantages. There is much repetition under the various headings. The clinical descriptions are sketchy. One cannot use the book as a reference text on vascular disease. For example, the index contains no reference to the treatment of chronic venous insufficiency or the

treatment of peripheral arterial embolism.

Despite these shortcomings, the authors have provided a good summary of current knowledge of the peripheral circulation.

N.L.

CLINICAL ENDOCRINOLOGY. By KARL E. PASCHKIS, M.D., ABRAHAM E. RAKOFF, M.D., and ABRAHAM CANTAROW, M.D. Jefferson Medical College of Philadelphia. 2nd ed. Pp. 941; 274 ills. New York: Paul B. Hoeber, Inc., 1958. Price, $18.00.

THIS is the second edition of a successful textbook in endocrinology; the format is similar to the first edition, excepting that it has been brought up-to-date. Clinical aspects of endocrinology are well presented with good correlation between signs and symptoms, and basic endocrine physiologic mechanisms. The list of references is sufficiently complete to suggest valuable reading for students. Of particular interest is the section on the Placenta, and Hormonal Findings of Pregnancy, physiologic and clinical information rarely available in textbooks. This book is considered to be eminently satisfactory for students and clinicians alike.

W.P.

A TEXT-BOOK OF X-RAY DIAGNOSIS. By BRITISH AUTHORS. Edited by S. COCHRANE SHANKS, M.D., F.R.C.P., F.F.R., Director, X-Ray Diagnostic Department, University College Hospital, London and PETER KERLEY, C.V.O., C.B.E., M.D., F.R.C.P., F.F.R., D.M.R.E., Director X-Ray Department, Westminister Hospital; Radiologist, Royal Chest Hospital, London. 3rd ed. Pp. 510; 553 ills. Philadelphia and London: W. B. Saunders Company, 1957. Price, $18.00.

THIS is Volume I of the 3rd edition of this text which is one of the two or three standard large comprehensive textbooks of X-ray diagnosis in the English language. Volume I deals with the central nervous system, the teeth and jaws, the eye, the accessory nasal sinuses, and the ear and temporal bone. The last edition of this work was published in 1950.

The present edition of Volume I differs from its predecessors. Part 1 on the central nervous system includes a discussion of the normal and pathological skull and its contents. The sections on encephalography and ventriculography and carotid angiography are comprehensive and a good general bibliography is provided.

The section on the eye deals only with foreign body localization. The section on the mastoids and temporal bone unfortunately does not go into the technique or the interpretation of a number of valuable special projections developed on the Continent and in Sweden, and now widely used in this country.

A good introductory bibliography is provided.

H.S.

CHIRURGIE D'EXÉRÈSE DANS LA TUBERCULOSE PULMONAIRE: TECHNIQUE, INDICATIONS, RESULTATS. By D. HONORÉ, Chief of the Department, University of Liege. Pp. 216; 11 ills. Paris: Masson et Cie, 1958. Price, 3.300 fr.

IN this book, Professor Honoré, who has had an extensive experience with pulmonary tuberculosis, reviews his results with 585 resections at the University of Liege during the 6-year period from 1949 to 1954. His experience appears to be similar to that of American surgeons in the same field. The operative technique used and the indications and pre- and postoperative care outlined are generally acceptable. There are 10 simple drawings of the pulmonary anatomy.

The major portion of the book is devoted to an analysis of the results obtained. The over-all results were commendable, with a low operative mortality and a high percentage of arrest of the disease. The great value of the study is in the analysis of the influence of the specific indication and degree of bacterial resistance to antimicrobial agents, upon the result obtained.

J.J.

THE RUDOLPH MATAS HISTORY OF MEDICINE IN LOUISIANA, VOLUME I. Edited by JOHN DUFFY, PH.D., Associate Professor of History, Louisiana State University. Pp. 522; 14 ills. Baton Rouge: Louisiana State University Press, 1958. Price, $10.00.

THIS book, the first volume of a comprehensive two-volume work, traces the medical history of Louisiana from the initial settlement in 1699 through the first quarter of the nineteenth century. In preparing this volume, the editor has drawn upon the rich historical collection gathered by the late Dr. Rudolph Matas, along with other available primary sources. Publication of the work has been made possible by a trust fund established by Dr. Matas in 1953.

Volume I presents an accurate and readable account of early medical practice in Louisiana. Dr. Duffy has prepared a unique study, fusing the historian's understanding

of the French, Spanish and American periods in Louisiana history with the health conditions of those times. The second volume, to follow, will bring this account up to the present century.

This definitive work will be especially interesting to students of American and medical history and to workers in public health. The book is attractive in composition, well illustrated, and includes a useful Bibliography and Index. F.R.

LE SYNDROME DE GUILLAIN-BARRÉ. BY R. COIRAULT, A. LARCAN ET P. DAVIDOU. Pp. 200. Paris: Masson et Cie., 1958. Price, 2000 fr.

THE form of polyneuritis with which this monograph is concerned is the subject of many controversial issues. Not even its title is a matter of general agreement. It is proper, therefore, that the subject be investigated from time to time in order to determine what light can be shed on the nature of the Guillain-Barré syndrome.

The authors divide the cases of this form of polyneuritis into two groups: (1) those of unknown cause, presumably the classical forms of the disease, and (2) secondary forms due to many causes. They recognize several forms of the disease: (1) spinal radicular, (2) spinal and mesencephalic, (3) pure mesencephalic, and (4) abnormal forms. They reject the concept that Landry's paralysis is a form of Guillain-Barré neuritis. The cause of the pure form of the disease cannot be determined on the basis of our present knowledge.

Among the secondary forms of the disease are included such causative factors as (1) toxic agents: mercury, ACTH, thallium, and triorthocresyl phosphate, (2) physical agents, (3) trauma, (4) infections, and (5) metabolic conditions.

This is a useful and well-reasoned monograph which records the controversial issues fairly, but which sheds no new light on cause or pathogenesis. The discussion of the secondary forms of Guillain-Barré polyneuritis is particularly valuable, and reveals convincingly the basis for regarding the disorder as a syndrome. The monograph will be found helpful to neurologists and internists. It can be warmly recommended. B.A.

CLINICAL OBSTETRICS AND GYNECOLOGY, JUNE, 1958, VOLUME 1, NO. 2. FIBROMYOMAS OF THE UTERUS. Edited by ROBERT A. KIMBROUGH, M.D., and TOXEMIAS OF PREGNANCY. Edited by LOUIS M. HELLMAN, M.D. Pp. 250; 47 ills. New York: Paul B. Hoeber, Inc., 1958. Price, $18.00 a year.

THE second book in the Hoeber quarterly series "Clinical Obstetrics and Gynecology" includes sections on the Toxemias of Pregnancy edited by L. M. Hellman and on Fibromyomas of the Uterus edited by R. A. Kimbrough. Each of the 31 contributors has a particular interest in the portion of the symposium prepared by him and in many instances has made outstanding contributions to our understanding of the specific problem.

In the section on Fibromyomas the various methods for diagnosing and treating the tumors are considered. Operative techniques for myomectomy and for vaginal and abdominal hysterectomy are described and a discussion on radiation therapy is included. The effect of the tumors on pregnancy is also considered.

Much of the section on toxemias of pregnancy is devoted to the physiologic changes which produce the characteristic signs and symptoms of the condition. The alterations in fluid and electrolyte metabolism in renal function, in hormone production, in uterine and cerebral circulation and in the vascular system in general are described. Prophylaxis against toxemia and treatment of preeclampsia-eclampsia and of hypertensive and renal disease are discussed.

In general this volume is well prepared and edited. The presentations are interesting, informative, practical and adequately illustrated with charts, line drawings, roentgenograms and photographs. It should prove valuable as a means by which practicing physicians, both obstetricians, gynecologists and others, can obtain authoritative up-to-date information on the subjects considered. J.W.

THE BIOLOGY OF HAIR GROWTH. Edited by WILLIAM MONTAGNA AND RICHARD A. ELLIS. Arnold Biological Laboratory, Brown University, Providence, R.I. Pp. 520; illustrated. New York: Academic Press, Inc., 1958. Price, $15.00.

THE Biology of Hair Growth, a volume produced by a group of experts in this field, illustrates how concentrated study of a single element of a complex organ such as the skin may produce so much information. The content of this volume consists of papers presented at a Conference on the Biology of Hair Growth, sponsored by the British Society for Research on Aging, which was held

at the Royal College of Surgeons in London on August 7, 8 and 9, 1957, supplemented by other material. It is intended to serve as a source reference for all those interested in research on hair and hair growth. Space does not allow full listing of all the subjects covered but they range from the embryology of hair to the aging of the human scalp. It is a well-illustrated, documented and indexed storehouse for almost every aspect of the anatomy, chemistry and factors affecting hair growth. Many of the subjects deal with man but some are concerned with certain animals. Montagna's summary ties the material together. This collation alone is worth the price of the book. In a field in which so much progress is being made, there is little to criticize, inasmuch as the authors are cognizant of the gaps in our knowledge and have not made elaborate, unwarranted claims. This book should serve as a stimulus to anyone interested in the subject of hair; physicians, veterinarians, and those interested in furs, textiles (wool) and hair products.

H.B.

Cerebral Vascular Diseases. Transactions of the Second Conference held under the Auspices of the American Heart Association, Princeton, N.J., January 16–18, 1957. Irving S. Wright, Chairman, Clark H. Millikan, Editor. Pp. 224. New York and London: Grune & Stratton, Inc., 1958. Price, $4.00.

Those who read the transcript of the First Conference have undoubtedly been looking forward to reading those of subsequent conferences, and this one will unquestionably live up to their high expectations. Gathered at the second meeting were 40 investigators who have been blazing a trail in the field of cerebral vascular disease. Included amongst these were Sir Russell Brain of London, Dr. Gustav Nylin of Stockholm, and Dr. Luis G. Sabathie of Rosario, Argentina. The topics covered included those of nomenclature, pathology, estimation of cerebral blood flow and cerebral blood pool, experimental disease and dysfunction, relationship of hypertension to cerebral vascular disease, intermittent cerebral ischemia, and therapy, including anticoagulants, enzymes, surgery and rehabilitation. Also included in the volume with the transcript of the Conference is the excellent Classification and Outline of Cerebrovascular Diseases prepared by an *ad hoc* Committee established by the Advisory Council for the National Institute of Neurological Diseases and Blindness, Public Health Service. The whole volume is highly recommended to all physicians since it contains much new information regarding basic mechanisms, diagnosis and therapy in a field in which very promising advances are being made. T.D.

Administrative Medicine: Transactions of the Fifth Conference, October 29, 30 and 31, 1956, Princeton, New Jersey. Edited by George S. Stevenson, M.D., National and International Consultant, National Association for Mental Health, New York, N.Y. Pp. 197. New York: Josiah Macy, Jr. Foundation, 1958. Price, $3.75.

The preface explains the goal of the multidiscipline approach to urgent problems in the field of medicine and health by a conference group of 28 participants, experts in their respective fields of Administrative Medicine. The conference covers 2 days.

The theme of this conference is Mental Health. Subjects discussed were Mental Health Elements in Administration of General Health, The Administrative Role in the Management of a Mental Hospital and the Co-ordination of Local Resources.

The informal presentation of each subject, the interruptions by participants in the form of questions, criticisms, or comment, and general discussion are recorded and published verbatim.

Inasmuch as there is no summary of stated subjects, this book must be read thoroughly to realize the importance and scope of the problems presented. The book has an autobiographical sketch of participants, references, and index.

Should be of considerable interest to all persons in the field of Administrative Medicine. D.S.

To Work in the Vineyard of Surgery: The Reminiscences of J. Collins Warren, 1842–1927. Edited, with appendices, notes, and comments, by Edward D. Churchill, M.D. Pp. 288; 3 ills. Cambridge: Harvard University Press, 1958. Price, $6.00.

This book possesses a triple interest, appealing both to a wide range of physicians and to historians and general readers. It is concerned chiefly with a member of one of the most noted medical families in America—Massachusetts and Pennsylvania being the best exemplars of this characteristic—the younger John Collins being fifth in the list of 6 generations of the medical Warrens. I have found the annotated list on page IX a

useful guide amid the Johns and Jonathan, especially in the earlier chapters. The book's title, which J.C.W. took from William Clowes, a 17th century "Maister in Chirurgerie," is an apt choice for one whose life extended from the discovery of ether (when he was only 4 years old, to be sure) through one of the most fruitful periods of surgical advances. Anesthesia was destined to "conquer" pain, though its progress still continues. The way to control infection was outlined and well explored for many applications that are still being developed for both medical and surgical diseases. Perhaps most important of all was the sound concept of pathology, "the study of the nature of disease," that had been firmly established during J.C.W.'s professional lifetime. It is now so developed that gross and microscopic anatomy, microbiology, physiology, biochemistry and biophysics, and mathematics are all contributing vigorously to medical progress, and most departments of a University or Research Institute nowadays are so equipped at least to a considerable extent.

Of the 23 chapters, the longest, on 19th Century Boston and its Surgery, starts with such details as the early geography of the town, through pictures, items such as "fixed basins," archaic bathtubs, and rather primitive boys schools, eventually reaching the M.G.H., of which the first J.C.W. was a co-founder with James Jackson and the second J.C.W. on the active staff for 45 years. He noted the need for new activities, mentioning 6 of the returning pupils of Louis (Bowditch, Jackson, Shattuck, Holmes, Hooper and Mason Warren) but deplored the lagging and lamentable state of operative surgery. (See his article on a Century of Surgery, 1896.) The chapter ends with his entrance into Harvard College and a report of his meetings with Simpson (of chloroform fame) and Civiale, the inventor of the lithotrite.

The footnotes by E. D. Churchill, here (as throughout the book) are found on almost every page and are voluminous, being considerably longer than the text itself. Conveniently differentiated by a smaller type, without restriction of topic, and prepared by an experienced investigator who has observed widely and writes with charm and humor, these notes and comments to the reviewer constituted the more valuable part of the book. In fact, it is not an overstatement to add that they lift an often rather sluggish manuscript to an unusually entertaining level. This should not be regarded in any way as a slur on the ability of the author of the reminiscences. He had a long and successful surgical career that was recognized by the honors bestowed on him at home and abroad, and was "a greatly respected clinical surgeon, competent at the operating table and in the consulting room alike." As he himself expressed it in an unpublished letter to Harvey Cushing, "I have been a sort of John the Baptist, preaching in the wilderness, and I am counting on you as the surgical Messiah." J.C.W. was the prophet preparing the way, Cushing one of many who formed a sort of collective Messiah. Here it might be added that disproportionate space has been given to this one chapter as a sample of what might have been expected throughout the book.

J.C.W.'s most important service to the Harvard that his family has served so well for two centuries was his persistent and eventually successful advocacy with Henry P. Bowditch of the "great undertaking on Longwood Avenue." The steps leading to the establishment of this new Harvard Medical School in 1906 are fully described in the last section of the Reminiscences. Three appendices, written by the Editor, give a Biographical Supplement, an account of The Start on the Cancer Problem (by the Cancer Commission), and a retrospect and a forward look, entitled: Two Cycles of Medicine at Harvard: 1846–1906, 1906– . With our taste buds stimulated by the Editor's glimpses into the future of medical progress, we can highly recommend this book to the physicians, historians, and general readers mentioned in the first sentence of this review. E.K.

ACTION OF RADIATION ON TISSUES: AN INTRODUCTION TO RADIOTHERAPY. By A. LACASSAGNE AND G. GRICOUROFF. Translated by CLARENCE C. LUSHBAUGH, M.D., AND GRETCHEN R. RIESE, M.S., University of California (Los Alamos Scientific Laboratory). Pp. 199; 17 ills. New York: Grune & Stratton, Inc., 1958. Price, $6.25.

THIS is the first English translation of a small book which has become a classic since its publication in French in 1941.

The mechanisms of radiation injury and their manifestations, are first discussed at the cellular level, then at the connective tissue level. A series of short but detailed chapters on radiation effects on each of the normal tissue systems follows, with a concluding chapter on effects on pathologic tissues.

The book is so concise, complete and readable as to establish itself at once as mandatory for every medical library, and

certainly for every physician interested in radiation therapy or radiobiology. An excellent bibliography, supplemented by the translators, is included.

The book is an invaluable addition to the literature; many printings are to be expected, in the next of which some small errors in translation and usage will, it is hoped, be corrected. R.R.

A Stereoscopic Atlas of Human Anatomy, Section IV, The Thorax. By David L. Bassett, M.D., Stanford University, with photography by William B. Gruber. Pp. 290; 280 ills. Portland, Oregon: Sawyer's, Inc., 1958. Price, $16.50.

This section of the Bassett Stereoscopic Atlas of Anatomy is the fourth of a projected eight sections. It consists of 140 stereo pairs of color photographs of dissections of the thoracic region with a well labeled black and white explanatory diagram for each stereo pair. When viewed through the proper viewer, each pair of pictures becomes a three-dimensional dissection available for study. Both the dissections and the photography are excellent and the selection of views is more than adequate to provide material for study which is second only to actual specimens. The fact that dissections of the heart and the lungs were done with the organs *in situ* adds definite interest.

J.H.

Clinical Radiology of Acute Abdominal Disorders. By Bernard S. Epstein, M.D., The Long Island Jewish Hospital, New Hyde Park, New York. Pp. 352; 406 ills. Philadelphia: Lea & Febiger, 1958. Price, $15.00.

The title Clinical Radiology of Acute Abdominal Disorders is a somewhat misleading one, the text actually covering a much broader field than that suggested by "Acute Abdominal Disorders." There are four chapters. Chapter 1 deals with congenital disorders and a large segment of this chapter is concerned with pediatric problems. Chapter 2 covers neoplastic diseases (of the stomach, small and large bowel, liver, pancreas, spleen, peritoneal and retroperitoneal spaces). Inflammatory disorders make up a large component of Chapter 3, (ulcerative colitis, gastric and duodenal ulcers, pancreatitis, and others). Chapter 4 includes "other subjects not covered elsewhere in the book" (traumatic disorders, foreign bodies and effects of drugs). The book discloses the wide range of interest of the author, who is also author of the text, "The Spine." Appended to each section is a bibliography, allowing the student to delve for more detailed information. The illustrations are good. The text reflects the mature experience of the author in radiologic diagnosis. On the whole, despite the wide subject coverage, this is not a hodge-podge work, and should serve as a ready reference or as an orientation text for the radiologist and clinician. H.W.

Callander's Surgical Anatomy. By Barry J. Anson, Ph.D., Professor of Anatomy and Walter G. Maddock, M.S., M.D., Professor of Surgery, Northwestern University Medical School. 4th ed. Pp. 1157; 1047 ills. Philadelphia and London: W. B. Saunders Company, 1958. Price, $21.00.

The authors have again succeeded in presenting a fine textbook which is of considerable value not only to surgeons but to all physicians. The basic plan of the text has been retained and many new and excellent drawings have been added.

The section dealing with the anatomy of the breast has been expanded considerably, especially as regards the newer concepts of cancer spread and lymphatic drainage.

The latest anatomical data pertaining to the diaphragm are reviewed, and their relationship to esophageal hiatal hernia is stressed.

The subjects of congenital cardiovascular lesions, funnel chest deformity, autonomic nervous system and varicose veins have all been brought up-to-date to meet the demands of recent interest and progress.

This work represents a true anatomical pillar in every medical library. D.D.

Modern Trends in Gastro-Enterology. Second Series. Edited by F. Avery Jones, M.D., F.R.C.P., Physician to Central Middlesex Hospital. Pp. 416, 146 ills. New York: Paul B. Hoeber, Inc., 1958. Price, 16.00.

The text includes 24 chapters which, as the title implies, deal with subjects of current interest in gastroenterology. More than that, each subject is dealt with by an expert, most of whom reside in the United Kingdom but also included are such authorities as H. L. Bockus, E. Buchman, J. B. Kirsner, B. Pernow, W. L. Palmer, J. Waldenstrom and others. Many of the contributors such as W. I. Card, J. N. Hunt, S. Sherlock and I. J. Wood have written texts on the subjects

they discuss so well and so cogently in their respective chapters. The subject coverage is broad. Included are chapters on basic physiology as well as chapters on diagnosis and treatment. Some of these sections such as those on collagen diseases, steatorrhea and blind loop syndrome bring together groups of diseases with refreshing clarity. Other chapters are designed to bring the reader up-to-date on such ever present problems as peptic ulcer, regional enteritis, ulcerative colitis and carcinoma. Still other chapters are devoted to discussions of newly recognized problems such as carcinoid tumor and the lower esophagus lined by columnar epithelium.

Professor Jones is to be commended on the excellence of both subject matter and authorship. I am certain that all students of medicine and surgery will find the reading of this book a rewarding experience. S.L.

DERMATOLOGIE UND VENEROLOGIE. BAND 11, TEIL 2. BY H. A. GOTTRON AND W. SCHÖNFELD. Pp. 670; approximately 277 ills. Stuttgart: Georg Thieme Verlag, 1958 (Intercontinental Medical Book Corporation, New York, U.S. Agents). Price, $36.65.

VOLUME 2, number 2, continues the high level presentation of number one. It contains indexes of authors and subject matter presented in both parts one and two. Volume two, part two, discusses: Diseases of unknown cause classified according to their morphology; papular skin diseases (lichen ruber planus and lichen nitidus); hemorrhagic diseases; atrophies; scleroderma and scleroderma-like diseases. Diseases of known cause: Parasitic skin diseases; mycoses of the skin, coccal diseases; sarcoidosis; acute vacillary diseases and zoonosis; virus diseases of the skin and tuberculosis of the skin.

H.B.

GRUNDLAGEN EINER PHYSIOLOGISCHEN CHIRURGIE. BY PROF. DR. RENÉ LERICHE. Pp. 248. Stuttgart: Hippokrates Verlag, 1958. Price, DM28.60.

THIS book was published first in 1955 by Masson et Cie, Paris, under the title of Bases de la chirurgie physiologique—Essai sur la vie végétative des tissus. It was translated into German by Priv. Doz. Dr. med. R. Ch. Behrend. The book is not a pathological physiology, but it represents an appeal to surgeons to approach the therapy of disease processes via the vegetative nervous system. As therapy of this kind affects the mechanisms which regulate the biology of the various tissues, the knowledge of this kind of physiology is of paramount importance. The author, therefore, inquires into the modus by which in humans a disease changes tissues. Special attention is paid to the vegetative biology of arteries, veins, capillaries, sympathic and peripheral nerves, connective tissue, cartilage and bone, to the growth of tumors, and to the biology of pain. Arteriovenous anastomoses and thrombophlebitis are discussed in detail. In the last chapter methods of physiological surgery are discussed, namely the vasodilatory action of procain and operative procedures including operations for reactivation of endocrine glands. This stimulating book of a famous surgeon should be a valuable addition to the library of any physician. W.E.

PHYSICO-CHIMIE BIOLOGIQUE ET MÉDICALE. BY CHRISTIAN BÉNÉZECH, of the Faculty of Medecine at Montpellier. Pp. 684; 235 ills. Paris: Masson et Cie, 1958. Price, 8000 fr.

THIS volume succeeds in building a bridge between the abstract physical chemical theories and laws and the practical aspects of their application to biology and medicine. The first part (102 pp.) of the book is devoted to a reasonably full development of the theoretical bases of the field, covering the topics of thermodynamics, reaction kinetics, and the electronic structure of matter (including a discussion of stable and radioactive isotopes of interest in medicine and biology).

The second part (211 pp.) considers the laws governing the behavior of matter in its three forms, gases, liquids and solids and applies these laws especially as they relate to homogeneous aqueous solutions, of materials of biological interest such as plasma, urine, transudates, and others. It contains an excellent presentation of the spectrophotometric study of biological pigments, hemoglobin and its derivatives in particular.

The third part (126 pp.) describes the phenomena included under the general term "colloidal," including surface tension, adsorption, ion exchange and the like. The fourth part (187 pp.) applies the previous material to the study of plasma and the intra- and extracellular fluid. The energy exchanges and enzymatic reactions of living tissues are also described. Finally, the exchange reactions in the lungs, kidneys, digestive tract and between the cells and the extracellular fluids are discussed, along with regulatory mecha-

nisms involved in physicochemical homeostasis.

The printing and the physical appearance of the book are excellent, as is usual with these publishers. We can only hope for the appearance of an English translation which would make possible its more widespread appreciation in this country. J.B.

THE URETEROVESICAL JUNCTION. By JOHN A. HUTCH, M.D., University of California. Pp. 168; 96 ills. Berkeley and Los Angeles: University of California Press, 1958. Price, $7.50.

THIS book is a complete study of the ureterovesical junction in health and disease. It is written specifically for the urologist and features the author's new concept about the cause and management of the distressing problem of reflux of urine up the ureters in various pathological states. The book gathers together all of the pertinent information about reflux that has been previously published. The illustrations are excellent, the book is clearly written and, whether one agrees or not with the author's ideas about reflux, this volume is a reading must for all urologists. T.H

THE NEUROLOGIC EXAMINATION. By RUSSELL N. DEJONG, M.D., Professor of Neurology, University of Michigan Medical School. 2nd ed. Pp. 1078; 368 ills. New York: Paul B. Hoeber, Inc., 1958. Price, $20.00.

IN this book, Professor DeJong first presents the anatomy and physiology of the central and peripheral nervous system and correlates this with the findings in the neurologic examination. Changes in structure and function are outlined and these in turn are correlated with abnormalities in the examination.

The author places special emphasis on sensory disturbances of central origin and changes that occur with involvement of the parietal lobe and the thalamus. Advances in Neuro-ophthalmology and in the neurologic aspects of Otology are presented.

The author also presents the newer concepts of the reticular formation and the disturbances of sleep and consciousness and also the anatomic basis for psychomotor or temporal lobe epilepsy. Recent investigations concerning the formation, absorption, and circulation of the cerebrospinal fluid, as well as newly developed chemical and spectrophotometric methods of value in this examination are given in the chapter on spinal puncture and examination of the cerebrospinal fluid.

This book will be welcomed by neurologists, neurosurgeons, neurophysiologists, and particularly by the internists or the specialists interested in the neurologic aspects of disease. M.S.

Nuclear Magnetic Resonance. (Ann. New York Acad. Sci., 70, Art. 4, Pp. 763–930, 1958). By H. S. GUTOWSKY AND FREDERICK C. NACHOD, Conference Chairmen, and 16 Others.

THIS volume consists of a series of papers which were presented at a conference held by the New York Academy of Sciences in November, 1957. The phenomenon of magnetic resonance, requirements of instrumentation, and certain applications of this new investigative tool are discussed.

Workers in physical organic chemistry will be particularly interested in these fundamental dissertations. C.Z.

Year Book of Pathology and Clinical Pathology (1957–1958 Year Book Series). Edited by WILLIAM B. WARTMAN, B. S., M.D. Pp. 478; 171 ills. Chicago: Year Book Publishers, Inc., 1958. Price, $8.00.

THIS book consists of brief abstracts of the great majority of papers published during the "series year" on subjects of interest in Pathology and Clinical Pathology. The editor has again performed an excellent service to workers in these fields, all of whom will find much information conveniently summarized in this small volume. C.Z.

The Physician's Own Library. By MARY LOUISE MARSHALL, Librarian, Rudolph Matas Medical Library, Tulane University. Pp. 87. Springfield, Ill.: Charles C Thomas, 1957. Price, $3.00.

THIS little volume gives some excellent advice on the planning of a library that will save the physician who follows it both space and money while he achieves a library suited to his particular needs and circumstances. There are also items on the arrangement and physical care of books and journals, library records, book loan services available to physicians and even some instructions on the writing of medical articles. Since the advice which this book offers is most useful to the recent medical graduate, more is the pity that so small a book (not 75 pages of text) is so expensice. R.K.

Die Wirbelsäule in Forschung und Praxis. Band 5. Störungen in der Entwicklung und Leistungsfähigkeit der Wirbelsäule. Edited by PROF. DR. MED. HERBERT JUNGHANNS. Pp. 99; 55 ills. Stuttgart:

Hippokrates-Verlag, 1958. Price, DM 29.50.

THIS is a series of nine lectures by various authors who discuss the spine including its embryology, congenital anomalies, structure and significance of the suspension of the spinal cord, congenital anomalies of the spinal cord, the peripheral neurological examination in diseases of the spinal cord, kyphosis, the cervical spine in thigh amputees, the indications for laminectomy in lumbar disk hernias and functional phenomena due to static changes in the spinal column.

O.K.

A Classified Bibliography of Gerontology and Geriatrics. Supplement 1, 1949–1955. BY NATHAN W. SHOCK, Chief, Gerontology Branch, National Heart Institute, National Institutes of Health, and the Baltimore City Hospitals. Pp. 525. Stanford, Calif.: Stanford University Press, 1957. Price, $15.00.

THIS volume is the first supplement to the original Bibliography of Gerontology and Geriatrics which covers the literature up to and including 1948. The enormous increase in the publications in this field is shown by the fact that almost as many articles appeared in 1949–1955 inclusive as in the preceding 49 years. References, numbering 15,983, are arranged in a well planned manner that is clearly set forth in the 16 pages of the Table of Contents. All workers in gerontology and geriatrics will be most grateful to Doctor Shock for this signal service.

R.K.

International Standards for Drinking-Water. Pp. 152. Geneva: World Health Organization, 1958. Price, $4.00.

THE need for some form of international agreement and cooperation on regulations for safe and potable water supplies has grown apace with the great increase in travel, especially air travel, where carriers must be watered at many places in the world and travelers furnished with a safe and acceptable drinking-water. The answer to that need has been furnished by the World Health Organization in formulating this set of minimal standards. There are sections on Bacteriological Requirements, Chemical and Physical Requirements, Biological Requirements, Radiological Requirements, Laboratory Facilities for the Examination of Water, and Suggested Subjects for Research Investigations. There are Annexes on data that should accompany samples, the Computation of MPN Index (most probable number of organisms per 100 ml.); Approved Methods for the Bacteriological Examination of Water, Chemical Analysis and Biological Examination. This is an important new contribution of the World Health Organization.

R.K.

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